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

Technical Document

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Technical Document Section 3.4: Systematic Reviews: Mood Stabilisers and Antiepileptics

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Mood Stabilisers and antiepileptics

Identification of primary trials on the use of mood stabilisers and antiepileptics 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 3June 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 mood stabilisers and antiepileptic medication review:

85. exp Anticonvulsive Drugs/
86. exp lithium/
87. exp carbamazepine/ or exp chloral hydrate/ or exp clonazepam/ or exp diphenylhydantoin/ or exp nitrazepam/ or exp oxazepam/ or exp pentobarbital/ or exp phenobarbital/ or exp primidone/ or exp valproic acid/ or exp acetazolamide/
88. exp lithium carbonate/
89. (carbamazepine or divalproex sodium or depakote or keppra or gabapentin or lamotrigine or lithium or oxcarbazepine or phenytoin or sodium valproate or valproic acid or ethosuximide or levetiracetam or phenobarbital or primidone or tiagabine or topiramate or vigabatrin).tw.
90. or/85-89
91. 84 and 90
92. limit 91 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	67	19	39
Medline	189	73	142
Embase	410	42	312
Cinahl	111	5	41

Selection process

Search 1:
The searches yielded 777 citations altogether. Checking through these resulted in 692 exclusions due to duplication, title and abstract. The remaining 85 citations were subjected to criteria assessment which led to a further 48 being excluded, 14 put aside in a box due to small sample size and the full text was required for 12. 11 of the citations could not be excluded on title and there were no abstracts available for these. These citations were submitted to the GDG members for scrutiny and based on group consensus, 4 were excluded, another 4 were added to the box and it was necessary to obtain the full text for 3.

Overall, 15 full texts were obtained of which 9 failed to meet the inclusion criteria, the reasons for these exclusions are given in table 7. 2 were found to be relevant but included a sample size of less than 10 and so were boxed.

A breakdown of the selection process for this search is shown in figure 9.

Search 2:
The databases yielded 139 citations in total including controlled trials to case series. All citations were scanned to ensure that no controlled trials would be missed. It was identified nevertheless that the majority of citations were indeed case series and so a quick scan through these resulted in 137 eliminations from the search on the basis of duplication, title and abstract alone. In addition to the 2 remaining citations, a further 4 full texts for citations previously suggested by investigators in the field, were required for further examination.

A breakdown of the selection process for this search is shown in figure 10.

Search 3:
This search produced 534 citations altogether including case series to controlled trials. All citations were scanned to ensure that any relevant controlled trials would not be overlooked. None of these were suitable for inclusion and were all excluded solely based on duplication, title and abstract.

A breakdown of the selection process for this search is shown in figure 11.

Results: Included studies

Search 1:
In the end, 4 articles and a further 1 study discovered from a book qualified for data extraction and quality assessment. Hence, only 5 studies satisfied the inclusion criteria for this review.

The one controlled trial (Tyrer *et* al, 1993) revealed for inclusion in this review was extracted from a book and focused on the effectiveness of lithium in the management of behaviour problems in adults with a learning disability.

The other four studies included one retrospective case series study also associated with the effects of lithium (Langee *et* al, 1990). There was one prospective, case series study looking at the effects of valproate (Verhoeven *et al*, 2001) and another retrospective, case series study also on valproate (Ruedrich *et al*, 1999). The fourth included study retrospectively attempted to identify whether the antiepileptic medication topiramate would prove useful in improving behavioural problems in adults with a learning disability (Janowsky *et al*, 2003).

An overview of the characteristics of these studies is provided in table 8.

Search 2:
On full text scrutiny, 1 study was excluded the reason for which is also given in table 7. 2 studies were 'boxed' due to relevance but small sample size and data extraction and quality assessment was completed for 3 studies that fulfilled the inclusion criteria for this search.

Two of the included studies explored the effects of lithium, one of which consisted of adults and children with the results for both reported together and so was included as a controlled trial in adults and children (Tyrer *et al*, 1984) and the other in adults only (Craft *et al*, 1987). The third relevant study was on carbamazepine (Reid *et al*, 1981).

An overview of the characteristics of the studies in adults for this search is also provided in table 8 and for the 1 study in adults and children, in table 9.

Figure 12 shows a summary of the studies found across the 3 searches in this review.

Figure 9: Search 1 – Mood stabilisers/ antiepileptics

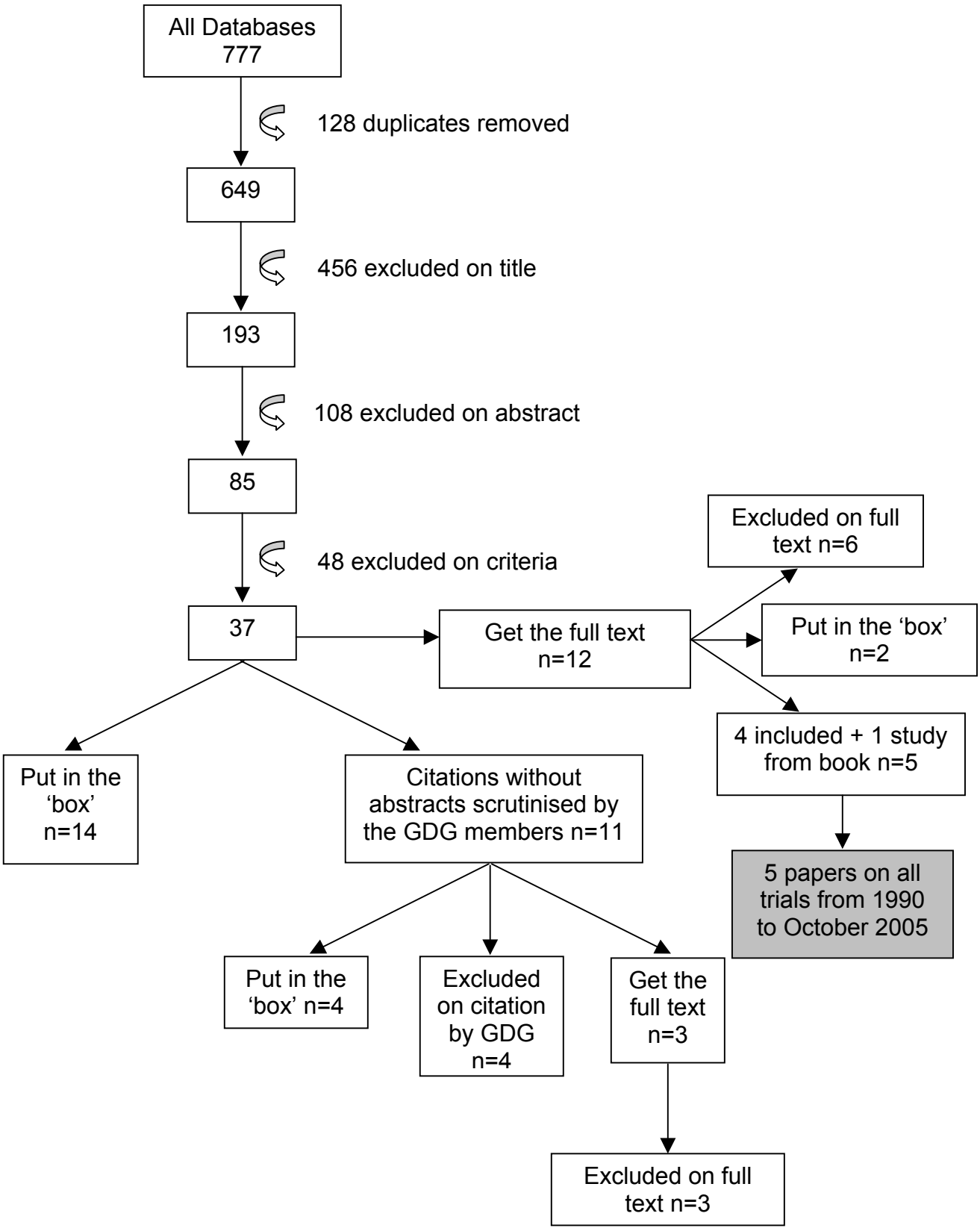


Figure 10: Search 2 - Mood Stabilisers/ antiepileptics

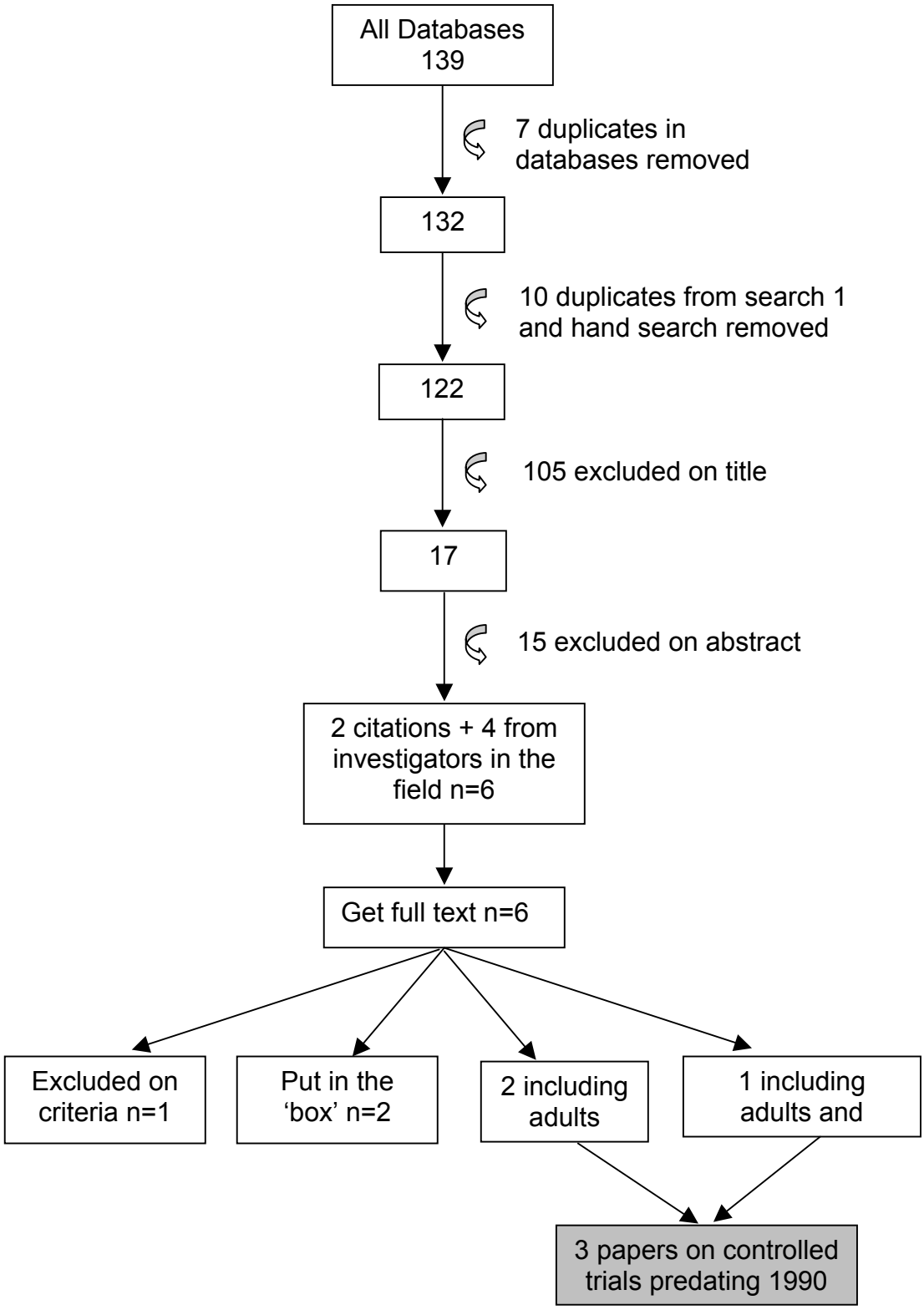


Figure 11: Search 3 - Mood Stabilisers/ antiepileptics

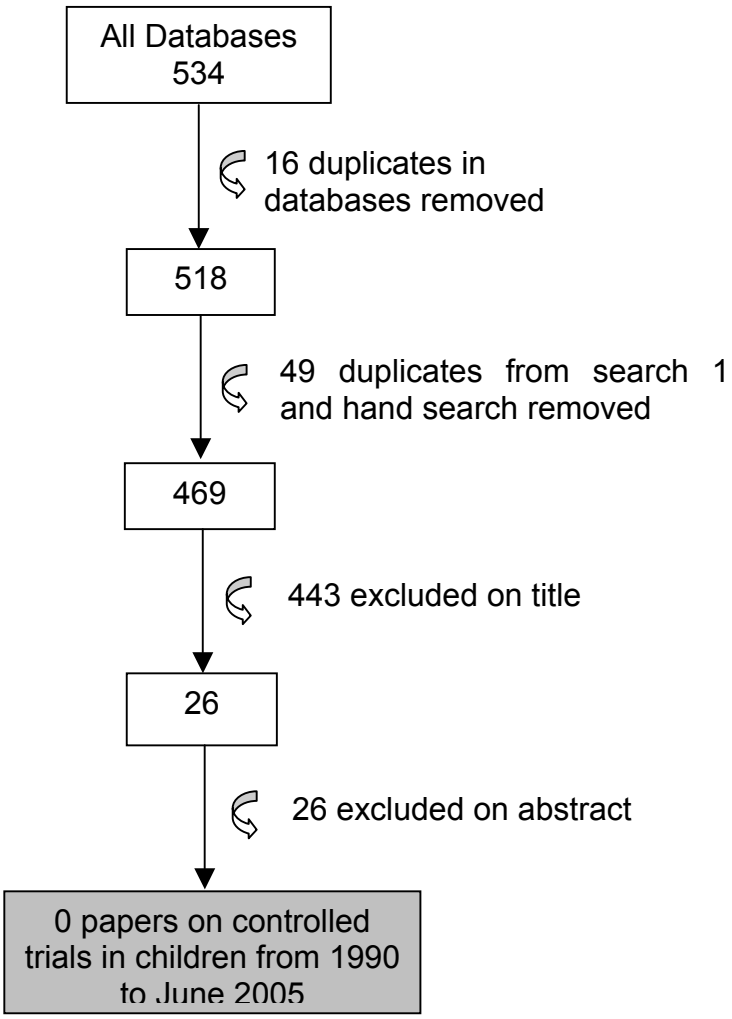
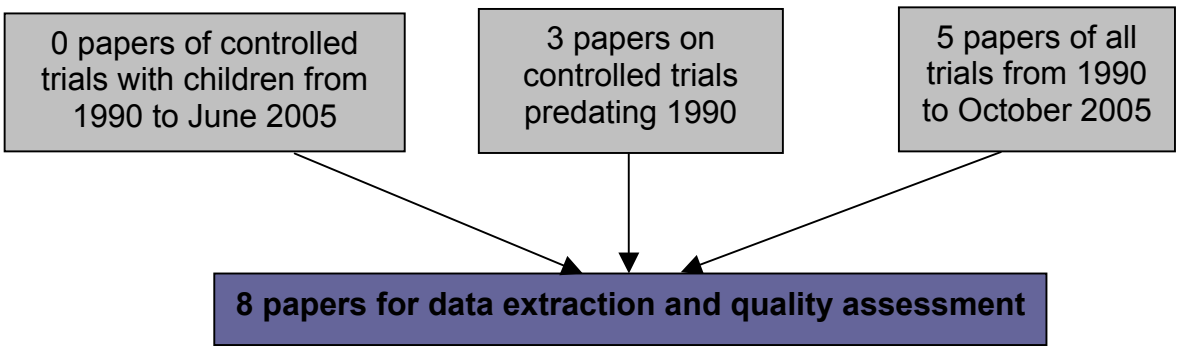


Figure 12: Summary of the mood stabilisers search



Mood Stabilisers/ antiepileptics review: summaries of included studies

Controlled trials

Adults

Tyrer et al. (1993)

Participants
52 inpatients, age range 24-51 years (gender ratio unknown). All participants were described as "mentally handicapped". Participants presenting with 4 episodes of aggression per month for 3 months or self-harm sufficient to cause physical damage or damage to property were included. Those with a co-morbid psychiatric diagnosis other than unipolar or bipolar illness were included.

Method
A prospective, double blind, placebo-controlled, cross over trial.

Intervention
One month of placebo for all at the start of the trial, then either Lithium carbonate as add-on, initially 500mg per day adjusted to achieve plasma levels of 0.5-0.8mmol/l or placebo followed by a crossover phase.

Follow-up
Participants were assessed every two weeks. The overall length of follow-up was 5 months (1 month placebo, 2 months on lithium and 2 further months on placebo).

Outcomes
The nurses and investigators carried out the following assessments:

1. Visual analogue scale (VAS) rating behaviour on 11 domains (including physical aggression, self-injury etc).
2. Blood tests: FBC, U&E, Creatinine and Thyroxine were taken every two weeks during the trial to monitor effects of lithium toxicity.
3. EEGs.

Results
Of the 52 patients, 2 dropped out before completion due to deterioration in behaviour. 15 of the 50 (30%) who completed showed a marked improvement and could be managed in a different setting. 13 (26%) improved but not enough to affect their residence or occupation. 22 (44%) did not improve. 5 (10%) patients became more aggressive on lithium compared to placebo. Lithium significantly reduced scores of physical aggression ($p<0.01$), posturing ($p<0.05$) and rebellious behaviour ($p<0.05$). Lithium did not affect non-physical aggression, self-injurious behaviour, destructiveness, temper tantrums or hyperactivity. There were no episodes of lithium toxicity.

Comments
Lithium has been shown to be of benefit in some areas of behaviour. The study population was well defined and the sample represents a very high percentage of those eligible. Blinding techniques have been adequately described. The paper was confusing when reporting overall behaviour changes and improvement in relation to the whole sample and did not differentiate whether this was a result of the lithium or placebo treatments. Participants were receiving concomitant medications and this could have confounded the results. The study period was short and a crossover design makes the effects of lithium withdrawal another potential confounder. Inter-rater reliability was not considered appropriate, as numerous nurses were involved in recording the outcome measures. This study achieved 8/14 on quality assessment.

Craft et al. (1987)

Participants
42 hospitalised patients, age range 19-65 (69% male). 90% had severe a LD and 10% had mild. Participants presented with aggression (n=22; 52.4%), SIB (n=1; 2.4%) and both behaviours (n=19; 45.2%). Aggression however, was the only target behaviour investigated. Those already receiving lithium were excluded from the study.

Method
A RCT with a double blind, placebo-controlled design.

Intervention
Lithium carbonate initially 800mg/day adjusted to achieve plasma levels of 0.7-1.0mmol/l. Lithium was administered in n=22 (52%) and placebo in n=20 (48%). Any previous medications were continued throughout the trial.

Follow-up
Assessments took place daily by nursing staff for 12 weeks. The overall follow-up period was 4 months.

Outcomes
1. The level of aggression was recorded by means of a 5-point scale (1 = well behaved to 5 = seclusion required).
2. A mean weekly aggression score and the number of days with and without aggressive behaviour were recorded, as were any side effects.

Results
There was a reduction in aggressiveness in n=16 (73%), an increase in n=2 (9%) and no change in n=4 (18%) treated with lithium. 6 (30%) of the control patients had a reduction in aggression. Side effects (tremor, drowsiness, thirst, polyuria, inco-ordination and vomiting) were reported in 8 (36%) on lithium, one needing temporary discontinuation of lithium. No reports of lithium toxicity were noted. Side effects were reported by 4 (20%) of the

control patients. Three was calculated as the number needed to treat (NNT; confidence levels 1.6 to 10).

Comments
This study supports the use of lithium. Blinding and randomisation procedures have been adequately described and target behaviours were well defined, although there were no findings relating to SIB that was present in many of the participants. The sample size was small and the follow-up period was very short. Participants were taking concomitant medications the details for which are not provided and nor is there any data of any comorbid illness in the participants. The outcomes were measured very crudely without the use of any validated assessment tools. This study scored 11/14 on quality assessment (5/5 on Jadad criteria).

Reid et al. (1981)

Participants
10 adults (2 of the participants were under 18 years of age and so the data for them has not been reported here), age range 19-50 (20% male). 40% had a severe and 60% profound LD. 5/10 (50%) had epilepsy. Overactivity was the target behaviour.

Intervention
Carbamazepine initially 200mg/ twice daily as add-on, (adjusted to achieve a blood carbamazepine level of 25-42 mcg/l; average dose 25-26 mcg/l) vs. placebo tablets.

Method
A double blind, placebo controlled, cross over trial whereby the treatment period for each patient was compared with his or her control period. There were two 3-month periods of treatment with either placebo followed by carbamazepine or vice versa. There was a 3-week wash out period separating the two phases.

Follow-up
Nursing staff assessed participants twice a day throughout the study. The overall follow-up period lasted for a maximum of 7 months.

Outcomes
The primary outcome was behaviour according to clinical characteristics with participants divided into two groups - Group A: overactivity since childhood, distractible, some mood elevation; Group B: overactivity as part of a broader spectrum of problem behaviours (e.g. self injury, stereotypy). A single non-validated weekly mean behaviour score was conducted. Nurses rated each patient on a scale of –3 to +3 (a score of –3 indicated behaviour as 'worst I have known', 0 as behaviour as usual and +3 as behaviour 'best I have known').

Results
In group A (pure overactivity), 3/5 (60%) of the participants were significantly better on carbamazepine than placebo and 1 was withdrawn due to reasons unrelated to the medication. In group B (overactivity as a spectrum of behaviours), 2/5 (40%) participants were significantly better on placebo than carbamazepine and 1 was significantly better on carbamazepine than placebo. Participants in group A tended to show improvements whereas those in B deteriorated and these differences were statistically significant ($p<0.029$). Therefore, those with pure overactivity tended to respond to carbamazepine rather than those who exhibited it as a spectrum of behaviour problems. There was no difference in response between those with and without epilepsy.

Comments
The trial is not of sufficient quality to recommend the use of carbamazepine as it is too small and furthermore, uses a single, non-validated outcome measure. Concomitant medications were used and this could have confounded the results. Side effects were not systematically assessed. This study scored 6/14 on quality assessment.

Adults and Children

Tyrer et al. (1984)

Participants
26 participants, age range 14-50 (65% male). All had a LD and were inpatients in a psychiatric hospital. 8 (31%) had epilepsy. Inclusion criterion was 4 episodes of aggressive behaviour per month for 6 months. The target behaviour was aggression. Participants with an affective disorder were excluded.

Intervention
Placebo was given to both groups for a month. Then there was a two month period of lithium carbonate given at 500mg per day adjusted to achieve a blood level of 0.5-0.8 mmol/ litre or placebo, followed by a crossover phase. Lithium was given as add-on medication and anticonvulsants were kept constant throughout the study.

Method
A double blind, placebo-controlled, crossover design. Dummy lithium results were given to keep blindness.

Follow up
Follow-up intervals were not given, but it is assumed that participants were assessed at the end of each of the 2-month study periods. Overall duration of follow-up was 5 months.

Outcomes
1. Psychiatrist ratings of 13 behavioural items on a visual analogue scale.

2. Nurses made 20 behavioural ratings relating to aggression, hyperactivity, antisocial behaviour and destructiveness.
3. Seclusion episodes and accident reports were noted.

Results
Results were provided for 25/26 patients as one withdrew from the study. 17/25 (68%) patients made overall improvements on Lithium compared to placebo. Rhythmic movement and stereotypy ($p<0.05$) was the only factor in which significant improvement was made, although there were improvements of a non-significant nature relating to the other areas of behaviour that were considered in the ratings. There was no evidence of safety problems except a small increase in fit frequency was noted in one patient.

Comments
This study does not provide convincing evidence for the use of lithium to reduce aggression in people with a LD. The degree of disability of the participants is unknown. This was a small, controlled, crossover trial with poor non-validated outcome measures. There was a short period of follow-up and it is unknown whether there was a washout period during the crossover phase. This study scored 8/14 on quality assessment.

Prospective studies

Verhoeven et al. (2001)

Participants
28 adults, age range 18-66 years (64% male). All had a mild to severe LD (unknown how many were in each category). Those with a clear neuropsychiatric diagnosis (i.e. uni-/bipolar affective disorder, OCD) were excluded although some had experienced psychiatric illnesses in the past. 8 (29%) had epilepsy or a history of it. The following were the presenting problems: SIB 7 (25%), aggression 15 (54%), hyperactivity 13 (46%), disorganised behaviour 6 (21%), stereotypies 10 (36%) and impulsivity 7 (25%).

Intervention
Valproic acid 300-3000mg/day (average dose 1345mg/day) as add-on. There was no wash out period; concomitant medications were stable for 3 months before the study and remained this way over the first 12 weeks of treatment. With the exceptions of those on medication for epilepsy, all other concomitant medication was then tapered off over a period of 6 weeks to 3 months.

Method
Prospective, uncontrolled, case series study.

Follow-up
Participants were monitored bi-weekly by staff members. Overall follow-up period was 6 months in 7 participants and 12 months in the other 21.

Outcomes
1. Frequency and intensity of target symptoms were assessed using visual analogue scales bi-weekly. 2. CGI ratings were conducted at 3-monthly intervals and final evaluations made after 6 months or 12 months.

Results
Moderate or greater improvement (defined as a stabilisation of behaviour and mood) as assessed on CGI was established in 19/28 (68%) participants. 9/28 (32%) had minimal changes or no improvement. No major side effects were noted.

Comments
This study has the strength of being prospective however, there are considerable drawbacks of the uncontrolled design such as the lack of any blinding or randomisation procedures. The outcome measures were not validated and side effects were not systematically assessed. Follow-up was for a reasonable period. There was a lack of any routine safety monitoring. This study scored 7/9 on quality assessment.

Retrospective studies

Janowsky et al. (2003)

Participants
22 adults, age range 25-70 (36% male). 63% had a profound, 14% severe and 23% had a mixture of severe and profound LD. 41% were epileptic and 91% were diagnosed with mood disorders (including bipolar affective disorder). All presented with chronic severe challenging behaviour in the form of SIB, aggression and were destructive/disruptive.

Intervention
Topiramate 150-350 mg/day as an add-on (average dose 202mg/day). There was no wash out period prior to the study.

Method
Summaries of quarterly multidisciplinary Neuropsychiatric Behavioural Reviews were examined retrospectively.

Follow-up
Assessments were at 3 monthly intervals from 6 months before the treatment period to 6 months after treatment started; it therefore appears that the overall follow-up period was 12 months.

Outcomes
1. Unit Psychologists recorded cumulative target behaviours (frequency measure) leading to a worst behavioural score and

2. Global behavioural severity ratings (severity measure) were made by one of the investigators during case conferences.
3. Side effects were noted in the last case review.
4. Weekly weights and 6 monthly blood tests were obtained.

Results
Worst behaviour score decreased in 14/19 (74%), increased in 4 (21%) and was unchanged in 1 (5%) ($p<0.02$). Severity of behaviour improved in 7/11 (64%) with SIB, worse in 3/11 (27%) and unchanged in 1/11 (9%) ($p<0.01$). Severity of aggressive behaviour improved in 9/16 (56%), became worse in 5/16 (31%) and was unchanged in 2/16 (13%) ($p<0.02$). Destructive behaviour decreased in 6/8 (75%) and increased in 2/8 (25%) ($p<0.26$). 5 cases of side effects were reported including one of hypoglycaemia, one of sedation, one of delirium and two of constipation. 'Several were observed to become less animated and less verbal' and weight was determined to be neutral.

Comments
Bias is introduced by the retrospective nature of this study. There was no analysis based on 'intention to treat' as results were only presented for 19 of the 22 patients; it is unknown about what happened to the other 3 participants. Outcomes were determined by what was reported in the case notes and so no validated outcome measures were considered. Furthermore, subjectivity bias may have been present as evaluations made by unit psychologists varied from individual to individual. There was no clear exclusion criterion. All participants were receiving other psychotropic medication and co-morbid psychiatric illnesses such as bipolar disorder, which could have influenced the results. This study scored 3/9 on quality assessment.

Reudrich et al. (1999)

Participants
28 adults, age range 20-63 years (54% male). 14% had a mild, 25% moderate, 25% severe and 36% profound learning disability. The participants had been on valproate for reasons other than epilepsy. 43% had seizure disorder and 21% had psychotic disorders. Target behaviours were primarily aggression in 93% of the participants, SIB in 64%, temper tantrums in 43%, rituals in 36% and sexually inappropriate behaviour in 14%.

Intervention
Divalproex or valproic acid 500-4000mg/day (average dose 920mg/day) as add-on, with no wash out period. All had previously taken other treatments. Participants had been on treatment for 2-73 months (mean 25.7 months). 19/28 (68%) received residential and 9/28 (32%) home treatment.

Method
A retrospective review of the investigators' experience of valproate in adults with a LD.

Follow-up
Follow-up was monthly from 2-73 months.

Outcomes
Two methods were used to assess the effectiveness of valproate: monthly behaviour counts were used in 17/19 of the participants whom were on residential treatment and the CGI-Severity scale was retrospectively applied for all 28 participants.

Results
Aggression and SIB decreased in 15/17 (88%) on residential treatment and 2/17 (12%) got worse. There were significant reductions in the monthly behaviour counts for aggression and SIB combined from 265 to 63 incidents per month (p=0.006). Overall, moderate or greater improvement was seen in 20/28 (71%), mild improvement in 6/28 (21%), 1 patient did not change and 1 deteriorated. Other medications were discontinued in 13/28 (46%) and reduced in 11/28 (39%). Side effects reported were intolerance in 1 patient due to gastrointestinal symptoms and 1 with thrombocytopaenia.

Comments
This was a retrospective and uncontrolled study where two different preparations of valproate were used, as well as two different samples of participants (residential vs. home treated). All were taking other treatments, there was no wash out period, and so the effects of other medications may have confounded the results. Strong outcome measures were not used and varied between the two samples. Side effects were not systematically assessed. Overall, the study is of extremely limited value and scored 3/9 on quality assessment.

Langee (1990)

Participants
66 adults, age was given separately for 'responders' (mean 39±13) and 'non-responders' (mean 32±9). 59% were male altogether. Participants had a severe to profound LD but it is unknown how many were in each category. 41% had co-morbid seizure disorder. All had failed to respond to antipsychotics in the past. The target was a behaviour problem that was severe enough to cause pain on a daily basis or tissue damage more than once a week, such as aggression, SIB and hyperactivity.

Intervention
Lithium carbonate initial dosage unknown but adjustments were made to achieve stable plasma levels of 0.7-1.2mmol/l. There was no wash out period and other treatments were allowed during the study period.

Method
This was a retrospective study in participants prescribed lithium over a 10-year period and for whom detailed case records were available.

Follow-up
Participants were followed-up at 3-monthly intervals.

Outcomes
The severity and frequency of target behaviours was recorded based on scales that were dependent on charted behaviour data and then these two scales were combined to give the 'behaviour disturbance index' of severity x frequency. This indicated the response to treatment. Staff was extensively trained in relation to detecting side effects early.

Results
31/66 (47%) were classified as 'responders' as determined by an improvement in their behavioural index scores. Logistic regression analysis showed that older patients with higher 'social ages' had better response rates. 24 of the 'responders' required additional psychotropic medication. 35/66 (53%) were classified as 'non-responders' as they showed no benefit of treatment. Side effects were mild and reversible - 2 had renal function deterioration, which was reversible on lithium discontinuation.

Comments
Although a 10-year study period was good, this study is limited because it is retrospective. Furthermore, there was no blinding or control group for comparison. The outcomes were not assessed using validated, standardised measures. The behaviour problems are variable and other than seizure disorder, it is unknown whether the participants had any co-morbid psychiatric illnesses. This study scored 5/9 on quality assessment.

Table 7: Studies excluded on full text

Study	Summary	Reason for exclusion
Brodtkorb, 2004	This was an open study examining levetiracetam for seizure control in patients with (n=56) and without (n-=128) a LD. Participants with a LD reported more behavioural problems with medication.	The intervention was given for seizure control, behaviour was reported as a side effect.
Carta, 2001	This was an open trial of gabapentin administered as an adjunctive therapy to 10 participants with a LD and bipolar spectrum disorders. Anxiety and depressive symptoms responded positively to gabapentin.	The intervention was given for the treatment of bipolar spectrum disorders in participants with a LD, rather than for a behaviour problem.
Friedman, 1992	This study explored carbamazepine associated behavioural adverse effects. 65 participants with a LD receiving carbamazepine for seizure control and/ or psychiatric illness were identified. 6 participants, 4 of whom were adults were identified who had experienced adverse behavioural changes with medication. These effects were reversible on discontinuation.	The primary outcome was adverse effects. Behaviour problems were reported if they emerged as one of the adverse effects.
Harper, 1993	This was a survey type study looking at the use of psychotropic and anticonvulsant medication in various settings for behaviour problems in 87 adults with a LD. It was identified that adults with a moderate disability living in larger settings were more likely to use medication than those living in smaller settings.	There was no specific medication intervention in this study and the outcomes were related to the prevalence of medication use.
Laminack, 1990	This was a letter reviewing an earlier retrospective study conducted before 1990 exploring the effects of carbamazepine. This letter indicated the potential drawbacks with the original study in response to the presented results.	This was a letter and not an article reporting on a new trial.
Mazzeo, 1994	This was a case series study in Italian showing that it may be necessary to revise the diagnosis 'Behavioural disorders in Mental Retardation' to 'Organic Disorder of Personality' and also the need to change the classic neuroleptics to Valpromide or Valproic Acid.	The purpose of this study was to indicate the changes required in making diagnostic decisions.
Mullerova, 1974	This was a clinical trial of lithium in 20 participants with a LD. There was some improvement in sociability/ adaptability but also some associated effects of unmotivated euphoria in two, and relatively deep depression in one participant.	This was not a controlled trial and so did not merit inclusion in search 2.
Pary, 1991	This was a non-blinded, clinical trial determining the effects of lithium that led to its discontinuation and subsequent improvement upon withdrawal. 10/15 participants experienced lithium side effects. It was concluded that individuals with a LD might be just as prone to side effects with lithium treatment as the general population.	This study was investigating the side effects of lithium.

Table 7: Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Smathers, 2003	This was an open label study in which topiramate was administered to 8 participants, both adults and children, whom presented with Prader-Willi syndrome associated behaviour problems. Improved mood, less aggression, less obsessive-compulsive behaviours and more controlled behaviours were reported in all participants.	There were no separate results for those aged 18 years or over.
Vadney, 1994	This was an open trial of both depakote and depakene administered as an anticonvulsant in 77 individuals with a LD. Aberrant behaviour observations were also made. Both medications were equally effective in seizure management and no increase in aberrant behaviour was found.	The intervention was given for seizure control, which was the primary outcome. Behavioural changes were monitored as secondary adverse effects of medication.

Table 8: Studies included in the mood stabilisers/ antiepileptics review: Adults

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Tyrer 1993 EC II	Lithium 500mg adjusted to achieve 0.5-0.8mmol/l plasma levels	Aggression, SIB, destructive behaviour, tantrums, hyperactivity	Controlled, crossover	52	VAS	54% improved on lithium, 44% unchanged and 2 participants dropped out.
Langee 1990 EC III	Lithium dosage adjusted to achieve 0.7-1.2mmol/l plasma levels	Aggression, SIB, hyperactivity	Retrospective Uncontrolled	66	Behaviour disturbance index (severity x frequency)	47% improved of which 77% required additional medication and 53% remained unchanged.
Craft 1987 EC I	Lithium dosage adjusted to achieve 0.7-1.0mmol/l plasma levels	Aggression	RCT	Study group: 22, controls: 20	Scores of counts of frequency and severity of target behaviour	73% improved, 9% got worse and 18% remained unchanged. 30% improved on placebo.
Verhoeven 2001 EC III	Valproate 1345mg	SIB, aggression, hyperactivity, disorganised behaviour, stereotypies, impulsivity	Prospective Uncontrolled	28	VAS, CGI	68% showed some degree of improvement and 32% minimally improved or remained unchanged.
Ruedrich 1999 EC III	Valproate 920mg	Various but primarily SIB and aggression	Retrospective Uncontrolled	28	Monthly behaviour counts, CGI	71% markedly improved, 21% mildly improved, 1 remained unchanged and 1 got worse.
Janowsky 2003 EC III	Topiramate 202mg	Aggression, SIB, destructive/ disruptive behaviour	Retrospective Uncontrolled	22	Cumulative frequency recordings, global severity ratings	74% improved, 1 remained unchanged and 4 got worse.
Reid 1981 EC II	Carbamazepine 25-26 mcg/l	Overactivity	Controlled, crossover	10	Nurse's behaviour ratings	Overall, 40% improved on carbamazepine and 40% on placebo.

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, VAS: visual analogue scale, CGI: Clinical Global Impressions scale

Table 9: Studies included in the mood stabilisers/ antiepileptics review: Adults & Children

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Tyrer 1984 EC II	Lithium 500mg adjusted to achieve 0.5-0.8mmol/l plasma levels.	Aggression	Controlled, crossover	26	VAS, nurse behaviour ratings	68% improved on lithium.

Evidence Category - II: controlled study without randomisation, VAS: visual analogue scale

References for search 1

Included studies (N>10)

1. Janowsky DS, Kraus JE, Barnhill J, Elamir B & Davis JM. Effects of topiramate on aggressive, self-injurious, and disruptive/destructive behaviors in the intellectually disabled: An open-label retrospective study. *Journal of Clinical Psychopharmacology* 2003; 23 (5): 500-504.
2. Langee HR. Retrospective study of lithium use for institutionalized mentally retarded individuals with behavior disorders. *American Journal on Mental Retardation* 1990; 94 (4): 448-452.
3. Ruedrich S, Swales TP, Fossaceca C, Toliver J & Rutkowski A. Effect of divalproex sodium on aggression and self-injurious behaviour in adults with intellectual disability: A retrospective review. *Journal of Intellectual Disability Research* 1999; 43 (2): 105-111.
4. Tyrer SP, Aronson ME & Lauder J. Effect of Lithium on Behavioural factors in aggressive mentally handicapped subjects. In *Lithium in Medicine and Biology* 1993, Birch, Padgham & Hughes (eds.) Carnforth: Marius Press.
5. Verhoeven WMA & Tuinier S. Cyclothymia or unstable mood disorder? A systematic treatment evaluation with valproic acid. *Journal of Applied Research in Intellectual Disabilities* 2001; 14 (2): 147-154.

Relevant studies (N<10)

1. Bozikas V, Bascialla F, Yulis P, Savvidou I & Karavatos A. Gabapentin for behavioral dyscontrol with mental retardation. *American Journal of Psychiatry* 2001; 158 (6): 965-6.
2. Davanzo PA & King BH. Open trial of lamotrigine in the treatment of self-injurious behavior in an adolescent with profound mental retardation. *Journal of Child & Adolescent Psychopharmacology* 1996; 6 (4): 273-9.
3. Ettinger AB, Weisbrot DM, Saracco J, Dhoon A, Kanner A & Devinsky O. Positive and negative psychotropic effects of lamotrigine in patients with epilepsy and mental retardation. *Epilepsia* 1998; 39 (8): 874-877.
4. Fahs H & Beauquier-Maccotta B. Preventive rule of lithium in self-injurious behavior: Case report. *Encephale* 1999; 25 (2): 175-8.
5. Hanzel TE, Bauernfeind JD, Kalachnik JE & Harder SR. Results of barbiturate antiepileptic drug discontinuation on antipsychotic medication dose in individuals with intellectual disability. *Journal of Intellectual Disability Research* 2000; 44 (2): 155-163.
6. Hardan AY, Jou RJ & Handen BL. A retrospective assessment of topiramate in children and adolescents with pervasive developmental disorders. *Journal of Child & Adolescent Psychopharmacology* 2004; 14 (3): 426-432.
7. Hellings JA, Hossain S, Martin JK & Baratang RR. Psychopathology, GABA, and the Rubinstein-Taybi syndrome: A review and case study. *American Journal of Medical Genetics Neuropsychiatric Genetics* 2002; 114 (2): 190-5.

8. Jerome L. Prader-Willi and bipolar illness. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993; 32 (4): 876-877.
9. Kalachnik JE, Hanzel TE, Harder SR, Bauernfeind JD & Engstrong EA. Antiepileptic drug behavioral side effects in individuals with mental retardation and the use of behavioral measurement techniques. *Mental Retardation* 1995; 33 (6): 374-382.
10. Kastner T, Finesmith R & Walsh K. Long-term administration of Valproic Acid in the treatment of affective symptoms in people with mental retardation. *Journal of Clinical Psychopharmacology* 1993; 13 (6): 448-451.
11. Kastner T & Friedman DL. Verapamil and valproic acid treatment of prolonged mania. *Journal of the American Academy of Child & Adolescent Psychiatry* 1992; 31 (2): 271-5.
12. Kurita H & Nakayasu N. Brief report: An autistic male presenting seasonal affective disorder (SAD) and trichotillomania. *Journal of Autism & Developmental Disorders* 1994; 24 (5): 687-692.
13. Maruta K. Lithium intoxication in a patient with severe motor and intellectual disabilities. *No to Hattatsu [Brain & Development]* 2003; 35 (5): 422-425.
14. Mattes JA. Valproic acid for nonaffective aggression in the mentally retarded. *Journal of Nervous & Mental Disease* 1992; 180 (9): 601-602.
15. Nishimura H, Suzuki M, Kasahara H & Ushijima S. Efficacy of lithium carbonate on public and compulsive masturbation: a female case with mild mental disability. *Psychiatry and Clinical Neurosciences* 1997; 51 (6): 411-3.
16. Olson DA, Ingram W & Mann JR. Combination of olanzapine and divalproex for agitation in individuals with profound mental retardation. *Journal of Clinical Psychopharmacology* 2002; 22 (5): 529-530.
17. Shapira NA, Lessig MC, Lewis MH, Goodman WK & Driscoll DJ. Effects of Topiramate in adults with Prader-Willi syndrome. *American Journal on Mental Retardation* 2004; 109 (4): 301-309.
18. Shapira NA, Lessig MC, Murphy TK, Driscoll DJ & Goodman WK. Topiramate attenuates self-injurious behaviour in Prader-Willi syndrome. *International Journal of Neuropsychopharmacology* 2002; 5 (2): 141-145.
19. Singh AN. Fluoxetine treatment of self-injurious behaviour in mental retardation and its interaction with carbamazepine. *Journal of Drug Development* 1993; 6 (1): 23-4.
20. Verhoeven WMA, Boermans JAJ, Van Der Heijden F & Tuinier S. Psychosis following treatment with topiramate. *Nederlands Tijdschrift voor Geneeskunde* 2002; 146 (44): 2093-2095.

Excluded studies

1. Armour DJ, Fidler C, Wright EC & Balarajan S. Vigabatrin in adults with poorly-controlled epilepsy and learning disabilities. *Seizure* 1992; 1 (3): 157-62.
2. Barnhill J & Carlos A. Phenobarbital-induced disinhibition in the developmentally disabled: Case report. *Journal of Clinical Psychopharmacology* 1997; 17 (3): 229-230.

3. Beran RG & Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia* 1998; 39 (3): 280-282.
4. Bhaumik S, Branford D, Duggirala C & Ismail IA. A naturalistic study of the use of vigabatrin, lamotrigine and gabapentin in adults with learning disabilities. *Seizure* 1997; 6 (2): 127-33.
5. Bird JM & Joseph ZA. Levetiracetam in clinical use - A prospective observational study. *Seizure* 2003; 12 (8): 613-616.
6. Bremner AJ & Regan A. Intoxicated by water. Polydipsia and water intoxication in a mental handicap hospital. *British Journal of Psychiatry* 1991; 158 (FEB): 244-250.
7. Brodtkorb E, Klees TM, Nakken KO, Lossius R & Johannessen SI. Levetiracetam in adult patients with and without learning disability: Focus on behavioral adverse effects. *Epilepsy & Behavior* 2004; 5 (2): 231-235.
8. Brodtkorb E, Sand T & Strandjord RE. Neuroleptic and antiepileptic treatment in the mentally retarded. *Seizure* 1993; 2 (3): 205-211.
9. Carta MG, Hardoy MC, Dessi I, Hardoy MJ & Carpiniello B. Adjunctive gabapentin in patients with intellectual disability and bipolar spectrum disorders. *Journal of Intellectual Disability Research* 2001; 45 (2): 139-145.
10. Chisholm T & Morehouse RL. Adult headbanging: Sleep studies and treatment. *Sleep* 1996; 19 (4): 343-346.
11. Couper RTL & Couper JJ. Prader-Willi syndrome. *Lancet* 2000; 356 (9230): 673-675.
12. Crawford P, Brown S & Kerr M. A randomized open-label study of gabapentin and lamotrigine in adults with learning disability and resistant epilepsy. *Seizure* 2001; 10 (2): 107-115.
13. 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): 43-48.
14. Deb S & Hunter D. The effect of anticonvulsant medication on the psychopathology of adults with a mental handicap and epilepsy. *Human Psychopharmacology* 1992; 7 (2): 129-134.
15. Deb S & Joyce J. The use of antiepileptic medication in a population-based cohort of adults with learning disability and epilepsy. *International Journal of Psychiatry in Clinical Practice* 1999; 3 (2): 129-133.
16. Fennig S, Fennig S, Pomeroy J & Calev A. Developmental disorder, Tourette disorder and schizophrenia: A case study. *Israel Journal of Psychiatry & Related Sciences* 1997; 34 (3): 239-243.
17. Frenchman IB, Capo C & Kass H. Effect of treatment with divalproex sodium and lorazepam in residents of long-term-care facilities with dementia-related anxiety or agitation: retrospective chart review. *Current Therapeutic Research* 2000; 61 (9): 621-9.
18. Friedman DL, Kastner T, Plummer AT, Ruiz MQ & Henning D. Adverse behavioral effects in individuals with mental retardation and mood disorders treated with carbamazepine. *American Journal on Mental Retardation* 1992; 96 (5): 541-546.

19. Gaily E, Granstrom ML & Liukkonen E. Oxcarbazepine in the treatment of epilepsy in children and adolescents with intellectual disability. *Journal of Intellectual Disability Research* 1998; 42 (Suppl 1): 41-5.
20. Gaudenzi A, Rosati E, Chiocchetti B & Muscas GC. The use of Levetiracetam in patients with mental retardation or organic psychosis. *Bollettino Lega Italiana Contro L'Epilessia* 2003; 122: 177-178.
21. Hanzel TE, Kalachnik JE & Harder SR. A case of phenobarbital exacerbation of a preexisting maladaptive behavior partially suppressed by chlorpromazine and misinterpreted as chlorpromazine efficacy. *Research in Developmental Disabilities* 1992; 13 (4): 381-392.
22. Harbord MG. Significant anticonvulsant side-effects in children and adolescents. *Journal of Clinical Neuroscience* 2000; 7 (3): 213-6.
23. Harper DC & Wadsworth JS. Behavioural problems and medication utilisation. *Mental Retardation* 1993; 31 (2): 97-103.
24. Huber B, Bommel W, Hauser I, Horstmann V, Liem S, May T, Meinert T, Robertson E, Schulz L, Seidel M, Tomka-Hoffmeister M & Wagner W. Efficacy and tolerability of levetiracetam in patients with therapy-resistant epilepsy and learning disabilities. *Seizure* 2004 13 (3): 168-175.
25. Huber B & Tomka-Hoffmeister M. Limited efficacy of gabapentin in severe therapy-resistant epilepsies of learning-disabled patients. *Seizure* 2003; 12 (8): 602-603.
26. Iwasaki T, Miura H, Sunaoshi W, Hosoda N, Takei K & Katayama F. A case of intractable epilepsy showing frequent gelastic seizures by administration of clobazam. *No to Hattatsu [Brain & Development]* 2003; 35 (5): 406-10.
27. Kelly K, Stephen LJ & Brodie MJ. Pharmacological outcomes in people with mental retardation and epilepsy. *Epilepsy & Behavior* 2004; 5 (1): 67-71.
28. Kelly K, Stephen LJ, Sills GJ & Brodie MJ. Topiramate in patients with learning disability and refractory epilepsy. *Epilepsia* 2002; 43 (4): 399-402.
29. Khurana DS, Riviello J, Helmers S, Holmes G, Anderson J & Mikati MA. Efficacy of gabapentin therapy in children with refractory partial seizures. *Journal of Pediatrics* 1996; 128 (6): 829-33.
30. Laminack L. Carbamazepine for behavioral disorders. *American Journal on Mental Retardation* 1990; 94 (5): 563-564.
31. Langee HR. Carbamazepine for behavioral disorders (I: Reply). *American Journal on Mental Retardation* 1990; 94 (5): 564.
32. Leary PM & Allie S. A new drug suitable for children and young people with epilepsy and intellectual impairments. *Developmental Medicine & Child Neurology* 1995; 37 (4): 371.
33. Luiselli JK. A non-aversive behavioral-pharmacological intervention for severe self-injury in an adult with dual sensory impairment. *Journal of Behavior Therapy & Experimental Psychiatry* 1991; 22 (3): 233-8.
34. Matson JL, Luke MA & Mayville SB. The effects of antiepileptic medications on the social skills of individuals with mental retardation. *Research in Developmental Disabilities* 2004; 25 (2): 219-228.
35. Mavromatis M. The diagnosis and treatment of Borderline Personality Disorder in persons with developmental disability: Three case reports.

Mental Health Aspects of Developmental Disabilities 2000; 3 (3): 89-97.

36. Mayhew LA, Hanzel TE, Ferron FR, Kalachnik JE, & Harder SR. Phenobarbital exacerbation of self-injurious behavior. *Journal of Nervous & Mental Disease* 1992; 180 (11): 732-733.
37. Mazure CM, Druss BG & Cellar JS. Valproate treatment of older psychotic patients with organic mental syndromes and behavioral dyscontrol. *Journal of the American Geriatrics Society* 1992; 40 (9): 914-916.
38. Mazzeo A & Occhilupo A. Organic disorder of personality: Therapeutic response to valpromide and valproic acid. *Rassegna di Studi Psichiatrici* 1994; 83 (2): 129-136.
39. McGillivray JA & McCabe MP. Pharmacological management of challenging behavior of individuals with intellectual disability. *Research in Developmental Disabilities* 2004; 25 (6): 523-537.
40. McGuire JM, Baram V & Asher JM. Osteopenia associated with divalproex sodium. *Journal of Clinical Psychopharmacology* 2004; 24 (3): 357-358.
41. McKee JR, Sunder TR, FineSmith R, Vuong A, Varner JA, Hammer AE & Barrett PS. Lamotrigine as adjunctive therapy in patients with refractory epilepsy and mental retardation. *Epilepsy & Behavior* 2003; 4 (4): 386-394.
42. Mikati MA, Choueri R, Khurana DS, Riviello J, Helmers S & Holmes G. Gabapentin in the treatment of refractory partial epilepsy in children with intellectual disability. *Journal of Intellectual Disability Research* 1998; 42 (Suppl 1): 57-62.
43. Mirza WU, Credeur LJ & Penry JK. Results of antiepileptic drug reduction in patients with multiple handicaps and epilepsy. *Drug Investigation* 1993; 5 (6): 320-6.
44. Newberger DS & Blyth SA. Hypothermia and phenytoin toxicity. *Clinical Neuropharmacology* 2003; 26 (4): 172-173.
45. Ohtahara S & Yamatogi Y. Safety of zonisamide therapy: Prospective follow-up survey. *Seizure* 2004; 13 (suppl. 1): S50-S55.
46. Pary R. Side effects during lithium treatment for psychiatric disorders in adults with mental retardation. *American Journal of Mental Retardation* 1991; 96 (3): 269-73.
47. Poindexter AR. Phenobarbital, propranolol, and aggression. *Journal of Neuropsychiatry & Clinical Neurosciences* 2000; 12 (3): 413.
48. Roach ES, Delgado M, Anderson L, Lannaccone ST & Burns DK. Carbamazepine trial for Lesch-Nyhan self-mutilation. *Journal of Child Neurology* 1996; 11 (6): 476-8.
49. Sachdev PS. Psychoactive drug use in an institution for intellectually handicapped persons. *Medical Journal of Australia* 1991; 155 (2): 75-9.
50. Smathers SA, Wilson JG, Nigro MA. Topiramate effectiveness in Prader-Willi syndrome. Pediatric Neurology 28 (2): 130-133, 2003.
51. Smith C, Kerr M, Felce D, Baxter H, Lowe K & Meek A. Exploring the evaluation of antiepileptic drug change in people with intellectual disabilities and high-frequency epileptic seizures: seizure control and sustained responsiveness to the environment. *Epilepsy & Behavior* 2004; 5 (1): 58-66.

52. Sobanski T, Bagli M, Laux G & Rao ML. Serotonin syndrome after lithium add-on medication to paroxetine. *Pharmacopsychiatry* 1997; 30 (3): 106-107
53. Stenbom Y, Tonnby B & Hagberg B. Lamotrigine in Rett syndrome: Treatment experience from a pilot study. *European Child & Adolescent Psychiatry* 1998; 7 (1): 49-52.
54. Stolker JJ, Koedoot PJ, Heerdink ER, Leufkens HGM & Nolen WA. Psychotropic drug use in intellectually disabled group-home residents with behavioural problems. *Pharmacopsychiatry* 2002; 35 (1): 19-23.
55. Tiffin PA & Perini AF. The use of antiepileptic drugs in learning disabled people with epilepsy: An audit of adult in-patients in a treatment and continuing care service. *Seizure* 2001; 10 (7): 500-4.
56. Tobias ES, Brodie AF & Brodie MJ. An outcome audit at the epilepsy clinic: Results from 1000 consecutive referrals. *Seizure* 1994; 3 (1): 37-43.
57. Tsiouris JA, Cohen IL, Patti PJ & Korosh WM. Treatment of previously undiagnosed psychiatric disorders in persons with developmental disabilities decreased or eliminated self-injurious behavior. *Journal of Clinical Psychiatry* 2003; 64 (9): 1081-1090.
58. Vadney V, Ricketts RW & Cole RW. Effects on individuals with mental retardation of changing Depakote to Depakene. *Mental Retardation* 1994; 32 (5): 341-6.
59. Verhoeven WMA, Tuinier S, Van den Berg Y, Coppus AMW, Fekkes D, Pepplinkhuizen L & Thijssen JHH. Stress and self-injurious behavior; hormonal and serotonergic parameters in mentally retarded subjects. *Pharmacopsychiatry* 1999; 32 (1): 13-20.
60. Wroblewski BA, Joseph AB, Kupfer J & Kalliel K. Effectiveness of valproic acid on destructive and aggressive behaviours in patients with acquired brain injury. *Brain Injury* 1997; 11 (1): 37-47.
61. Xeniditis K, Russell A & Murphy D. Management of people with challenging behaviour. *Advances in Psychiatric Treatment* 2001; 7 (2): 109-116.

References for search 2

<u>Included studies</u>

Adults:

1. Craft M, Ismail IA, Kristnamurti D, Matthews J, Regan A, Seth V & North PM. Lithium in the treatment of aggression in mentally handicapped patients: A double blind trial. *British Journal of Psychiatry* 1987; 150: 685-689.
2. Reid AH, Naylor GJ & Kay DSG. A double-blind, placebo-controlled, crossover trial of carbamazepine in overactive severely mentally handicapped patients. *Psychological Medicine* 1981; 11: 109-113.

Adults and Children:

1. Tyrer, S, Walsh A, Edwards D, Berney T & Stephens P. Factors associated with a good response to lithium in aggressive mentally handicapped subjects. *Prog. Neuro-Psychopharmacology & Biol Psychiatry* 1984; 8: 751-755

Relevant studies (N<10)

1. Naylor G, Donald JM, Le Poidevin D & Reid AH. A double-blind trial of long-term lithium therapy in mental defectives. *British Journal of Psychiatry* 1974; 124: 52-57.
2. Worrall E, Moody JP & Naylor GJ. Lithium in non-manic depressives: antiaggressive effect and red blood cell lithium values. *British Journal of Psychiatry* 1975; 126: 464-8.

Excluded studies

1. Mullerova S, Novotna J, Rehan V & Skula E. Lithium treatment of behavioural disturbances in patients with defective intellect. *Activitas Nervosa Superior* 1974; 16 (3): 196.