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

Technical Document

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UNIVERSITY OF BIRMINGHAM
The Royal College of Psychiatrists
Let Wisdom Guide
MENCAP
Understanding learning disability

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Technical Document Section 3.3: Systematic Reviews: Antidepressants

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Antidepressants

Method

Identification of primary trials on the use of antidepressants 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 4 June 2005
Medline	1990 to week 1 Oct 2005	1966 to 1990	1990 to week 4 June 2005
Embase	1990 to 43rd week of 2005	1980 to 1990	1990 to 26th week of 2005
Cinahl	1990 to week 2 Oct 2005	1982 to 1990	1990 to week 4 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 antidepressant medication review:

85. exp Antidepressant Agent/
86. exp monoamine oxidase inhibitor/ or exp serotonin uptake inhibitor/ or exp tetracyclic antidepressant agent/ or exp tricyclic antidepressant agent/
87. (citalopram or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline).tw.
88. (amitriptyline or amoxapine or clomipramine or dosulepin or doxepin or imipramine or lofepramine or maprotoline or mianserin or nortriptyline or trazodone or trimipramine).tw.
89. (isocarboxazid or moclobemide or phenelzine or tranylcypromine).tw.
90. (mirtazapine or reboxetine or tryptophan or venlafaxine or nefazadone).tw.
91. exp TRICYCLIC ANTIDEPRESSANT DRUGS/ or exp ANTIDEPRESSANT DRUGS/
92. or/85-91
93. 53 and 84 and 92
94. limit 93 to (human and adulthood <18+ years> 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	82	26	36

Medline	180	54	68
Embase	364	26	157
Cinahl	391	29	292

Selection process

Search 1:
Of the 1017 citations retrieved altogether, 924 were clearly excluded based on duplication, title and abstract. A further 14 were excluded based on criteria scrutiny resulting in 79 citations for which a more methodical approach was needed before further exclusion, as it was necessary to obtain the abstracts for these. Of these, 29 were eligible but were put aside in a box because they included a sample size of less than 10. There was a lack of information available in the abstracts of a further 16 and so the full text was acquired for these. This process left 34 citations for which no abstracts were available and so these were submitted to the GDG members for scrutiny. The GDG members were able to exclude a further 17 based on title, 4 were kept in the box and the full text was required for the other 13.

In total 29 full texts were obtained of which 13 were excluded as they did not meet the inclusion criteria (the reasons for these are given in table 5) and 6 were 'boxed'. 2 studies revealed through hand search resulted in 1 being 'boxed' and 1 being excluded on full text. Data extraction and quality assessment was performed on the remaining 10 articles.

A breakdown of the selection process is shown in figure 5.

Search 2:
135 citations were produced altogether comprising of controlled trials to case series. In order to ensure that no controlled trials would be missed, all these citations were checked. The majority of the citations were excluded based on duplication, title and abstract, largely because of case study methodology and because antidepressants were given to treat depression rather than a behaviour problem. Only 2 articles eventually needed further inspection, 1 of which was yielded through earlier hand searching and the full texts of these were obtained for further scrutiny.

A breakdown of the selection process for this search is shown in figure 6

Search 3:
This search produced 553 citations altogether. As in search 2, most of the citations were removed based on duplication, title and abstract. There were 2 citations remaining for which a decision could not be made on the basis of abstract and so the full text was obtained for these. However, full text scrutiny ascertained that these studies were not suitable for inclusion either and so were consequently excluded. The reasons for excluding these latter 2 studies are given in table 5.

A breakdown of the selection process for this search is shown in figure 7.

Results: Included studies

Search 1:
Overall, the database searches revealed ten studies that fully met all the inclusion criteria for this review.

Of these studies, there was one RCT (Lewis *et al* 1995), which investigated the effectiveness of the tricyclic antidepressant clomipramine. The remaining studies explored the effectiveness of a range of Selective Serotonin Reuptake Inhibitors (SSRIs). Two cohort studies (Troisi *et al* 1995; Bodfish & Madison, 1993) and two open trials (Cook *et al* 1992; Markowitz 1992) looked at the efficacy of fluoxetine. Of the prospective case series studies, two were on fluvoxamine (La Malfa *et al* 2001; La Malfa *et al* 1997) and one on paroxetine (Davanzo *et al* 1998). In addition, there was one retrospective, uncontrolled study looking at paroxetine (Janowsky *et al* 2005) and one on both paroxetine and fluoxetine (Branford *et al* 1998).

Table 6 provides the overall characterisitics of these studies.

Search 2:
In the end, only one study was found that almost fulfilled the criteria for this search. The population for this study had a LD but included adults and children whereby the data for both was presented together. This was the only study in the antidepressants review that considered IM treatment and so it was decided that this study was not to be included (Carter *et al*, 1966). The reasons for excluding this and one other study on fulln text can be found in table 5.

Search 3:
No relevant articles were revealed for this search.

An overall summary of the findings for these searches is shown in figure 8.

Figure 5: Search 1 – Antidepressants

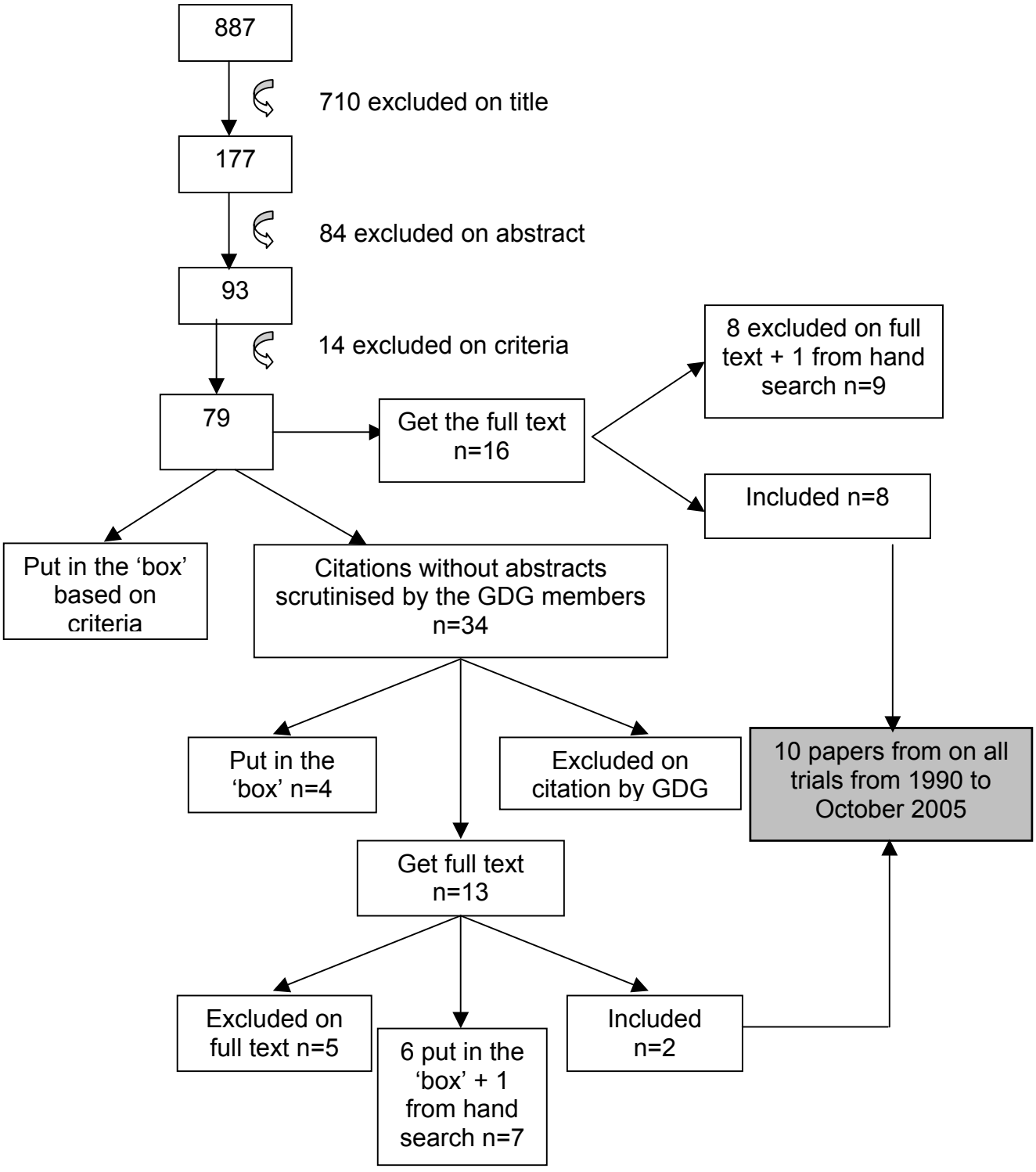


Figure 6: Search 2 - Antidepressants

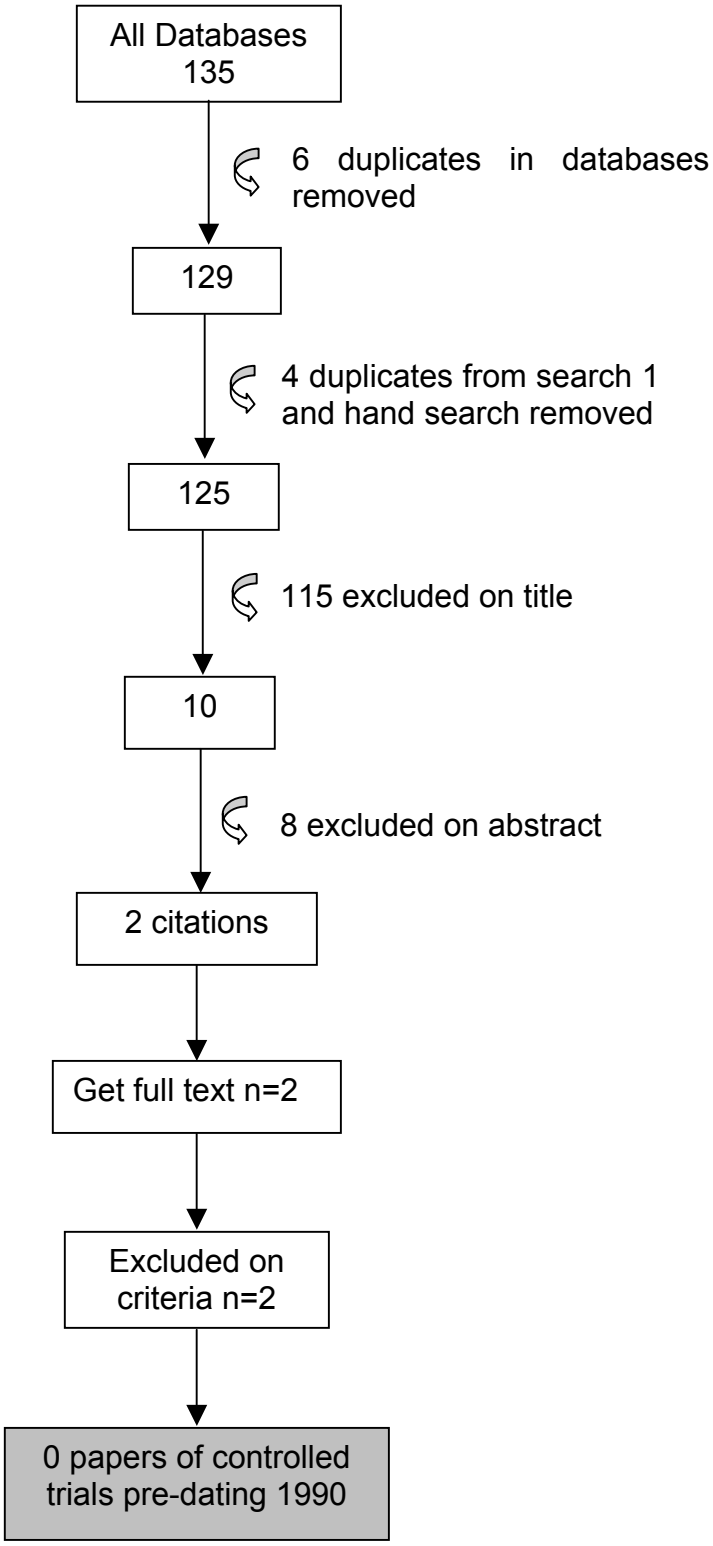


Figure 7: Search 3 - Antidepressants

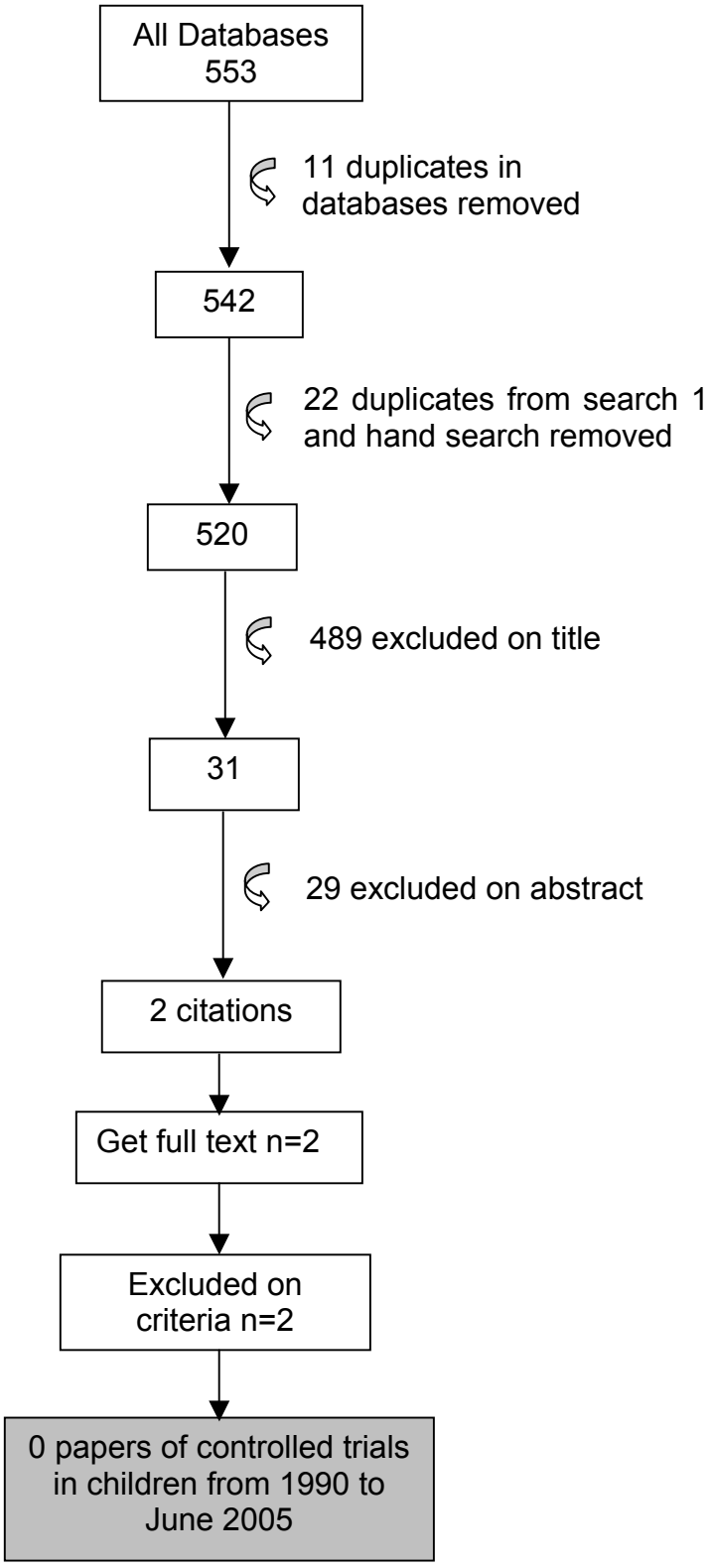
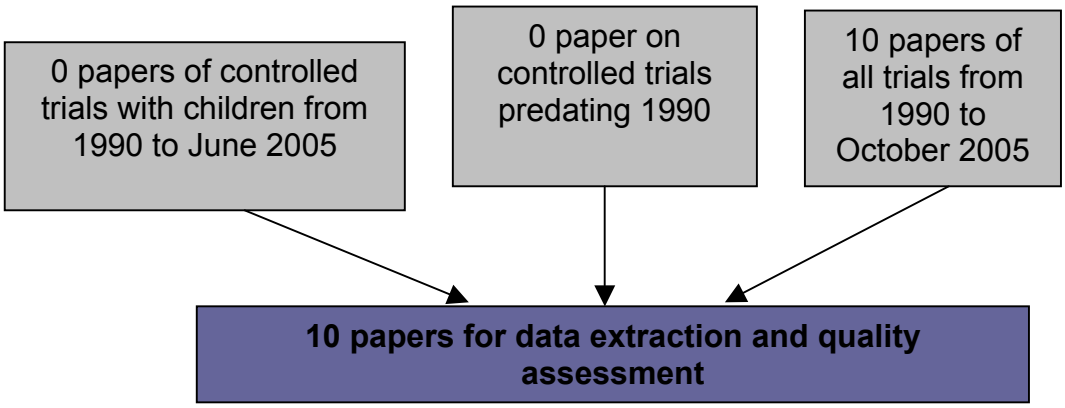


Figure 8: Summary of the antidepressants search



Antidepressants Review: Summaries of included studies

Controlled trials

Lewis et al. (1995)

Participants
10 adults, age range 18-42 years (80% male). 4 had a severe LD and 6 profound. 4 had autistic symptoms, 2 seizure disorder and 2 were taking concurrent antipsychotics for aggression. All participants presented with stereotyped (body rocking and object such as toy shaking, n=6), repetitive self-injurious (i.e. head hitting, n=5) and repetitive compulsive (checking, hording, arranging, touching, ordering etc., n=3) behaviours.

Intervention
Clomipramine the dose was titrated up to 225 mg/day (add-on in 4 participants) vs. placebo.

Method
A double blind, placebo controlled crossover study. The phases of the study were: single-blind placebo: weeks 1 and 2; double blind placebo vs. clomipramine: weeks 3-9 (titration stage – weeks 3 to 5; maintenance phase – weeks 6 to 9); titration down phase: week 10. Crossover second titration phase: weeks 10 to 12; second maintenance: weeks 13 to 16; second titration down phase: week 17 and final single-blind placebo: weeks 18 and 19.

Follow-up
Participants were observed on each of 3 or 4 days weekly. The overall period of follow-up was 19 weeks.

Outcomes
1. Teachers provided ratings on the ABC.
2. Staff provided ratings on a 5-point Likert scale for the intensity of repetitive behaviour. Nurses recorded side effects using the Treatment Emergent Side Effects Scale as a secondary measure.

Results
Improvement was observed in body stereotyped ($p<0.01$) and object stereotyped ($p<0.05$) behaviours. 3 (30%) developed adverse effects. 6 (60%) of the 7 who tolerated the medication exhibited a clinically significant improvement in one or more repetitive behaviours.

Comments
The small cohort does not provide enough power to the study. Crossover is not a good design because opposite results can be found across the 2 phases – pre- and post crossover. The outcome measure (staff rated Likert scale) is not validated. Although detailed results are given in the text of the study, the

graphs alone are difficult to understand and interpret. Furthermore, the target behaviours were part of obsessive-compulsive spectrum disorder for which clomipramine is indicated in any case. This study achieved 9/14 on quality assessment (4/5 on Jadad criteria).

Prospective studies

La Malfa et al. (2001)

Participants
60 Caucasian participants, average age 30.6±2.5 years (48% male). 67% had a mild LD and 33% had moderate. All participants presented with aggression and aversive behaviour. 92% were institutionalised inpatients and 8% lived with their family.
Intervention
Fluvoxamine was increased to 200-300mg daily (mean dose 250 mg/day). The starting dose was not stated.

Method
Prospective case series. There was a 1-week no medication period, followed by 2-weeks of placebo and then 3 weeks of medication.

Follow-up
Participants were assessed at the end of the first no medication week and then at the end of the placebo and 3-week fluvoxamine periods. Overall, duration of follow-up was 6 weeks.

Outcomes
Two experienced psychiatrists carried out all assessments. 1. The Handicaps, Behaviour and Skills Schedule (HBSs). 2. Side effects were measured using the Dosage Record and Treatment Emergent Symptom (DOTES) scale.

Results
There was a reduction in the severity of aggression with fluvoxamine than placebo ($p<0.001$) as demonstrated on the HBSs. No significant side effects were noted.

Comments
Fluvoxamine was more effective than placebo in reducing aggression. This was a preliminary trial published as a letter to the editor and therefore, understandably there were some important data missing such as any co-morbid diagnosis in the participants. The lack of rigour in the design of this study such as blinding or the use of a control group is a major drawback, as is the short follow-up period. This study scored 5/9 on quality assessment.

Davanzo et al. (1998)

Participants
15 adults, age range 30-56 years (33.3% male). 20% had a severe LD and 80% profound. All presented with aggression (biting, kicking, pushing, scratching, throwing objects, pulling hair, pinching) and SIB (head banging, biting self, choking self, hitting self, and pulling own hair).

Intervention
Paroxetine 10-50mg daily (mean dose 35mg). There was a 2-weeks washout period for 3 participants only. 8 were taking other medications throughout the study.

Method
Prospective case series.

Follow-up
Mean duration of the trial was 94 days. Participants were assessed at daily intervals and the overall follow-up period was 4 months.

Outcomes
Trained staff members (n=3) used standard behavioural observation techniques to assess frequency and severity of SIB and aggression.

1. Severity was rated using a 0-5 scale (0 = no occurrence of behaviour, 5 = life threatening).
2. Frequency of behaviour was logged.

Results
Only severity not frequency of aggression reduced over the 4-month period (p=0.027). The most beneficial effects of paroxetine were seen at 1-month follow-up and this was the case for the improvement seen in the severity of SIB (at 1 month: p=0.024). However, gains showed no statistical significance in the later months. People with anxiety disorders had greater symptom reduction than others and there was less improvement for females than males.

Comments
Paroxetine may only be useful in the short term. It is unclear on what 'trained' meant in relation to the staff carrying out the ratings and so subjectivity bias may be present. Inter-rater reliability between the raters was not tested and so this could have introduced bias and blinding was not employed. Although the rating scale has been described, it is unclear whether these were validated standard tools for behavioural assessment. This study scored 4/9 on quality assessment.

La Malfa et al. (1997)
Participants
14 adults, age range 24-40 years (57% male). All were diagnosed with either a severe or profound LD and exhibited aggression (hitting, pinching, biting,

verbal abuse, damage to property, throwing objects, unprovoked rage) and SIB (self hitting, self biting, head banging, picking at wounds, pulling own hair out) for the last 6 months.

Intervention
Fluvoxamine 300mg daily. There was a 2-week washout period whereby all psychoactive medication was withdrawn followed by 4 weeks of fluvoxamine treatment.

Method
Prospective case series.

Follow up
Participants were assessed at baseline, at 3-hourly intervals during the study and at 4 weeks. The overall duration of follow-up was 6 weeks.

Outcomes
1. Functional analysis for aggression at 3 hourly intervals and the following at baseline and after treatment:
2. CGI
3. Psychopathology Instrument for Mentally Retarded Adults (PIMRA).
4. Diagnostic Assessment for the Severely Handicapped (DASH - Italian translations).

Results
Functional analysis revealed a significant reduction in aggression compared to baseline ($p<0.01$). PIMRA and DASH total scores showed a slight reduction in target behaviours however these were not statistically significant. The DASH SIB score identified a significant reduction ($p<0.01$). The CGI score showed a significant reduction after 4 weeks of treatment ($p<0.01$). 3 of the participants experienced episodes of vomiting over the first week of treatment only.

Comments
There was no control group and the study was not blinded. The sample size was small and the follow-up period was short. The primary outcome measure of functional analysis has not been validated or tested for inter-rater reliability. The authors have stated that PIMRA and DASH measures were not validated. It is unknown who carried out the assessments and how many individuals were involved in this. This study scored 4/9 on quality assessment.

Troisi et al. (1995)

Participants
19 adults, age range 20-47 years (73.7% male). 13 (68%) had a severe LD, 2 (11%) had moderate and 4 (21%) had an unspecified LD. All had co-morbid epilepsy. The target behaviour was aggression.

Intervention
Fluoxetine 20 mg in the morning as an add-on for a length of 8 weeks in 10 participants and between 4-14 weeks for the other participants.

Method
Prospective longitudinal study using a control-treatment-control design. The study lasted a period of 8-26 (median 20) weeks pre-treatment, 8 weeks treatment phase and post-treatment 6-14 (median 8) weeks.

Follow-up
The participants were assessed daily during the treatment phase and the length of follow-up was a median of 36 weeks.

Outcomes
Care staff and a Clinical Psychiatrist using the Modified Overt Aggression Scale (MOAS) rated aggression.

Results
Medication brought about significant changes in total aggression ratings ($p<0.02$), verbal aggression ($p=0.03$) and self-aggression ($p<0.03$). In 9 cases in whom aggression deteriorated with fluoxetine, the behaviour improved after the withdrawal of this medication. Aggression deterioration was therefore seen in 9/19 (47%) cases, no appreciable change in 8/19 (42%) cases and some improvement in 2/19 (11%) cases.

Comments
Fluoxetine has been shown to have varying effects on aggression. No control group was used and the sample size was small. It is not known whether any of the participants experienced adverse effects and the MOAS is a subjective measure and so prone to bias. The authors have stated that there may have been an interaction between fluoxetine and concomitant medication and so may have been responsible for the negative impact on behaviour control. This study achieved 4/9 on quality assessment.

Bodfish et al. (1993)

Participants
16 adults, age range 21-43 years (69% male). 1 had a mild LD, 1 moderate and the rest had either a severe or profound LD. Compulsive behaviour disorder, self-injury (head hitting, self biting, eye poking) or aggression (hitting, kicking, or biting) were the main presenting problems. 5 participants had co-morbid epilepsy.

Intervention
Fluoxetine 20mg/ daily as add-on, increased incrementally by 20mg/ daily until a therapeutic response or ceiling of 80mg/ daily was reached. There was no washout period. 15 were taking neuroleptics and 1 was taking Benzodiazepine during the study.

Method
Prospective case series.

Follow-up
The study consisted of a 4-month baseline of individualised neuroleptics and behavioural management programmes. This was followed by a titration phase of 1-3 months and then 4 months on a minimally effective dose of fluoxetine.

Outcomes
Participants were monitored daily and monthly frequency recordings were also taken. An unspecified standardised outcome measure was used to measure target behaviour that required staff intervention. Staff documented discrete episodes of target behaviours and a psychologist checked the accuracy and compliance of recordings.

Results
7 (44%) of the participants were classified as responders to treatment as they had a substantial reduction in the target behaviour. Of non-responders, 9 (67%) had an increased mean level of target behaviour. No significant side effects were noted.

Comments
Although this study primarily targeted OCD related behaviours, there were specific outcomes reported for behaviour problems such as aggression and SIB, which merited this study for inclusion. However, there appears to be too many variables under examination. The neuroleptics were not withdrawn before treatment and this could have influenced the results. The sample size was small, blinding was not employed and the outcome measures were not validated. This study scored 3/9 on quality assessment.

Cook et al. (1992)

Participants
23 children and adults (age 7.3–52 years) with 10 adults where the target was a behaviour problem (50% male). 30% had a mild LD, 10% moderate, 40% severe and 20% profound. Those that were given medication for other reasons such as weight or sleep problems, were not considered for this review, nor were those with OCD as SSRIs are usually indicated for this. Of those included, 1 had bipolar disorder NOS, 1 anxiety disorder NOS and 6 impulse control disorder NOS. Target behaviours were perseverative behaviours ranging from SIB, aggression to complex rituals.

Intervention
Fluoxetine 20-80 mg/day as an add on. Treatment duration for the whole group was 7-467 days depending on therapeutic response.

Method
Prospective open trial.

Follow-up
Participants were assessed at baseline, during treatment and at discontinuation. Treatment duration for the whole group was 7-467 days depending on therapeutic response.

Outcomes
1. Treating clinicians used global CGI ratings of severity of illness.
2. CGI therapeutic efficacy ratings were used as side effect estimates.
3. Specific CGI ratings on perseverations, compulsions or rituals depending on the individuals' particular difficulties.

Results
There was CGI improvement in 6/10 (60%) and no improvement in 4/10 (40%) participants. More specifically the following was observed: decrease in compulsive ordering and rate of aggression in 1 participant, less irritable and agitation in 1, cessation of SIB in 2, less 'hyper' and better mood in 1 and aggression in 1.

Comments
Participants responded variably to treatment. This study was good in the sense that it separated the results for those with and without autism. However, the overall design of this study is poor. The CGI is a subjective measure and where utilised as a single, primary measure, cannot be regarded as adequately measuring any behaviour change. No control group was used and neither was blinding or randomisation employed. It is unknown whether concomitant medication was kept constant during the course of the study and as these were not withdrawn before fluoxetine treatment, they may have influenced the results. This study scored 6/9 on quality assessment.

Markowitz (1992)

Participants
20 adults, age range 24-56 (data for one participant who was 17 years of age is not included in this review); (50% male). 55% had a profound and 45% severe LD. 2 had OCD, 2 seizure disorder, 2 schizophrenia and atypical psychosis and 1 had bipolar disorder. Target behaviours were aggression, SIB such as head banging, hand biting, face slapping, restlessness, agitation, obsessive-compulsive behaviour and social relatedness.

Intervention
Fluoxetine 20-40 mg/day as an add-on for duration of a minimum of 3 months.

Method
Prospective open trial.

Follow-up
Participants were assessed after the first month to see if an increase in dosage was necessary and after a total of 3 months.

Outcomes
Responses to treatment were judged based on direct caretaker observation. Staff were asked to rate the response as positive change: 'a small amount', 'a large amount' or 'somewhere in between'.

Results
18/20 (90%) of the participants demonstrated a therapeutic response. Positive changes occurred in SIB, emotional lability and aggression. Marked improvement was seen in 12/20 (60%), moderate 4/20 (20%), mild 2/20 (10%), no improvement 2/20 (10%). Medication was stopped in 1 participant due to side effects of anorexia and weight loss.

Comments
Fluoxetine was seen as being an effective treatment for SIB and aggression. However, no validated outcome measures have been used. There is no control group and no blinding or randomisation was used. The sample size is small. No statistics have been presented to support the results. The target behaviours included obsessive-compulsive behaviours for which SSRIs are indicated. This study scored 4/9 on quality assessment.

Retrospective studies

Janowsky et al. (2005)

Participants
38 adults altogether on variable antidepressants, with 14 on the same medication paroxetine and so data for these 14 are presented. Age range 22-57 years (50% male). All had a profound to moderate LD. The target behaviours were maladaptive behaviours including aggression towards others, SIB, destructive behaviours and other behaviours or combinations of the above.

Intervention
Paroxetine 10-40mg. Other psychotropics were continued throughout the study.

Method
Retrospective analysis of quarterly neuropsychiatric behavioural reviews (NBRs).

Follow-up
6 months

Outcomes
1. Psychologists rated specific target behaviours during the NBR conferences and the frequency of these was evaluated by totalling the cumulative longitudinal graphed observations.

2. Investigators evaluated the overall global ratings using a 7-point global behavioural rating scale (measuring mild – severe symptoms). This scale paralleled the CGI Severity of Illness scale.
3. Specific maladaptive behaviours were also rated on a 7-point scale.

Results
Overall, antidepressant improvement continued over the 6-month study period. There was an overall decrease in the 'most severe behavioural score', which was statistically significant ($p<0.001$). Changes in the scores of the psychologists' aggression ratings were not significant, SIB ratings decreased significantly ($p=0.048$), as did destruction/ disruption ratings ($p=0.005$).

Comments
Antidepressants were shown to be effective in the management of maladaptive behaviours. However, this study was retrospective in design and the participants were on other psychotropics throughout the study, which could have influenced the results. The outcome measures are not validated and the cohort size is small. This study achieved 5/9 on quality assessment.

Branford et al. (1998)

Participants
33 adults, mean age 39 (sd 10.05) years (67% male). 70% had severe a LD. 10 (33%) of the participants had co-morbid epilepsy. The target behaviours were perseverative and maladaptive behaviours such as aggression, destruction to property and self-injury.

Intervention
37 treatment episodes between 1991-1996 of Fluoxetine 20-80mg (25/37 episodes) and Paroxetine 20-40mg (12/37 episodes) were considered. The participants were taking other medications at the time of SSRIs prescription.

Method
Retrospective case note analysis (medical and pharmacy notes).

Follow-up
–

Outcomes
A Psychiatrist and a Pharmacist made ratings by applying the CGI rating scale retrospectively.

Results
Overall SSRI analysis showed no benefit in 15/37 (40%), deterioration 9/37 (24%) and some reduction in perseverative and maladaptive behaviour in 13/37 (36%) treatment episodes. Side effects (vomiting, increased agitation, excessive drowsiness, hypomanic behaviour, increase in maladaptive behaviour such as aggression, insomnia and a variety of other symptoms such as rashes and increased seizures) in 13 instances were the reason for

medication withdrawal. No significant differences in effectiveness and tolerance between the two treatments were established.

Comments

This study demonstrated an effectively negative finding. It highlights the importance of considering adverse events when prescribing. It also indicates the problem of retrospective data collection and the difficulty in getting valid information from case notes. No control group was used or blinding and randomisation. The CGI is subjective and not a strong primary outcome measure, particularly if used retrospectively. CGI may primarily include improvement in obsessive-compulsive behaviours for which SSRIs are indicated. This study scored 4/9 on quality assessment.

Table 5: Studies excluded on full text

Study	Summary	Reason for exclusion
Aman, 1986	This was a RCT of 10 participants given Imipramine to manage either acting-out behaviours or affective symptoms. Behavioural deterioration was seen in both groups and gross motor activity significantly increased. In particular, the acting-out group became more active during play and the opposite was observed in the other group.	Only 5 participants were administered the medication for a behaviour problem, the remaining were for depressive-like symptoms.
Barak, 1995	A prospective case series study in which 11 adults with a LD received clomipramine for disabling ritualistic behaviour. 81.8% were rated between 'minimally' and 'much improved' following treatment.	Compulsiveness was the target behaviour for which clomipramine is indicated in any case. There was no behaviour problem per se.
Berman, 1992	This was a single case study of a lady with a mild LD. In addition, she also suffered from depression, for which she was put on many medications including Prozac. However, an adverse reaction to medications resulted in her admission to a psychiatric hospital.	The intervention was not given to treat a behaviour problem.
Carter, 1966	This paper reported two RCTs in 49 adults and children with a LD and 'disturbed' behaviour. Nortriptyline Hydrochloride was administered as IM. There were no significant differences between the medications either in terms of onset of tranquillisation, its duration or order of administration. All medications showed a faster and longer duration of action over placebo.	This was the only study in this aspect of the review that considered IM management.
Cassidy, 1992	This was a survey conducted to determine the use of fluoxetine amongst Prader-Willi Syndrome patients in the treatment of behaviour problems and depression. Fluoxetine was most effective in reducing tantrums and least effective in controlling obsessive-compulsive behaviour.	This was a survey and there was insufficient information available to merit inclusion.
Duker, 1991	This placebo-controlled study looked at the effects of fenfluramine on behaviour problems in 11 participants with a LD. Behaviour recordings were made which revealed a decrease in stereotypic and inappropriate behaviours.	Fenfluramine has been withdrawn in the UK and so this study cannot be included.
Friedman, 1996	A very short letter to the editor briefly mentioning the results of a previous study whereby fluoxetine was responsible for increasing aggressive behaviour in 9/19 adult inpatients with a LD.	There was insufficient information available to merit inclusion.
Hagerman, 1994	This was a survey examining the efficacy of fluoxetine in patients with Fragile X syndrome. 10/14 participants had an improvement in mood lability, panic attacks and outburst behaviour. 12/17 males treated for aggression, also improved.	There was data on Fragile X syndrome but no specific data on 10 participants with a LD.

Table 5: Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Langee, 1992	This was a retrospective, survey type study on the efficacy of prescribing heterocyclic antidepressants (HCAs) in a LD population. It was identified that in a selected number of cases, HCAs are substantially safer, with fewer serious side effects for the treatment of behavioural symptoms in people with a LD.	There was no specific intervention being given to treat a behaviour problem and hence no relevant outcome data.
March, 1998	This was a RCT with 187 children and adolescents with obsessive-compulsive disorder. Sertraline treated participants experienced greater improvement than did the placebo treated group. Side effects of insomnia, nausea, agitation and tremor were reported with sertraline.	The population did not have a LD.
Markowitz, 1990	This was a preliminary study in which fluoxetine successfully treated SIB in 8 participants with a LD.	This study has been expanded in more than 10 participants and is included in search 1 (Markowitz, 1992).
McDougle, 1996	This was a RCT including 30 adults with autism. 10 had an IQ score of below 70. Fluvoxamine was given to manage aggression and interfering repetitive thoughts and behaviour. Medication was found to be significantly more effective than placebo in treating behavioural problems.	Some participants did have an IQ level of below 70 however, the primary outcome measures were related to the autism syndrome rather than any behaviour problems per se.
McDougle, 1998	This was an open-label trial of sertraline in 42 adults with pervasive developmental disorders. Sertraline was effective in 24/42 participants mainly in the treatment of repetitive and aggressive symptoms.	There were 28 participants with some degree of a LD, however, there were no separate results for this population and as this was not a controlled trial, it did not warrant inclusion.
Posey, 2001	This was an open-label trial of mirtazapine in 26 adults and children with pervasive developmental disorders. 9/26 participants showed improvement in aggression, self-injury and hyperactivity, as determined by CGI ratings.	There were only 2 participants over the age of 18 years with a LD and there was no separate analysis for these two.
Selikowitz, 1990	This was a RCT of fenfluramine treatment of behavioural symptoms in 15 adults and children with Prader-Willi syndrome. Fenfluramine improved food related behaviour and decreased aggressive behaviour.	Fenfluramine has been withdrawn in the UK and so this study cannot be included.
Singh, 1998	A prospective cohort comparison study in 11 adults with a LD whom displayed SIB. Fluoxetine was given to 7 and fluvoxamine to 4 participants. Marked improvement was apparent in the severity and frequency of SIB in 91% of the participants.	There were two groups of participants on each of the SSRIs but there were not 10 participants on a single medication.

Table 5: Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Tsiouris, 2003	This was a prospective, open trial assessing whether psychotropic medication treatment of a previously undiagnosed psychiatric disorder would reduce the incidence of SIB. SIB in LD that is resistant to behaviour modification and environmental changes could be effectively managed by treatment of the underlying psychiatric disorders with appropriate psychotropics.	There is no single medication included in this study. The intervention was the diagnosis of an underlying psychiatric disorder and then the treatment of the identified disorder appropriately.
Verhoeven, 2001	This was a controlled study of citalopram in the treatment of depression in 20 adults with a LD. Citalopram was effective in reducing depressive symptomatology and preventing its recurrence after treatment for up to one year.	The medication was administered to primarily treat depressive symptoms rather than a behaviour problem.

Table 6: Studies included

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Troisi 1995 EC III	Fluoxetine 20mg	Aggression	Prospective Controlled	19	Modified Overt Aggression Scale (MOAS)	In 47% there was deterioration, 42% showed no appreciable change and 11% had some improvement.
Bodfish 1993 EC III	Fluoxetine dose range 20-80mg	Compulsive behaviour, SIB, aggression	Prospective Uncontrolled	16	Unspecified outcome measure; documentation of discrete episodes of target behaviour	44% were classified as responders. 67% of non-responders had increased mean level of target behaviour.
Cook 1992 EC III	Fluoxetine dose range 20-80 mg	Perseverative behaviours including SIB to complex rituals	Prospective Uncontrolled	23 but 10 applicable adults	CGI	60% improved, 40% showed no improvement.
Markowitz 1992 EC III	Fluoxetine dose range 20-40mg	Aggression, SIB, obsessive-compulsive behaviours, social relatedness	Prospective Uncontrolled	20	Direct caretaker observation	60% markedly improved, 20% moderately, 10% mildly, 10% had no improvement and 5% discontinued due to adverse effects.
La Malfa 2001 EC III	Fluvoxamine 250mg	Aggression, aversive behaviour	Prospective Uncontrolled	60	Handicaps, Behaviour, and Skills Schedule (HBSs), DOTES	Severity of aggression decreased with medication.
La Malfa 1997 EC III	Fluvoxamine 300mg	Aggression, SIB	Prospective Uncontrolled	14	3-hourly functional analyses, CGI, PIMRA, DASH	Functional analysis showed decrease in aggression and DASH SIB score showed reduction. CGI showed improvement after 4 weeks of treatment.

Evidence Categories - II: controlled study without randomisation; III: other non-experimental studies such as case series, SIB – self-injurious behaviour, CGI – Clinical Global Impressions scale, DOTES – Dosage Record and Treatment Emergent Symptom scale, PIMRA – Psychopathology Instrument for Mentally Retarded Adults, DASH – Diagnostic Assessment for the Severely Handicapped

Table 6: Studies included in the antidepressants review *(continued)*

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Lewis 1995 EC I	Clomipramine titrated up to 225mg	Stereotypy, repetitive SIB and compulsive behaviour	RCT Crossover	10	ABC, 5-point Likert Scale for intensity of repetitive behaviour, Treatment Emergent Side Effects Scale	Improvement was seen in body and object stereotype behaviours. 6 improved in 1 or more repetitive behaviours.
Janowsky 2005 EC III	Paroxetine dose range 10-40mg	Aggression towards others, SIB, destructive behaviours	Retrospective Uncontrolled	38 but 14 relevant	Psychologists' target behaviour ratings, 7-point rating scale for global and specific maladaptive behaviours	SIB and destruction/ disruptive behaviour ratings significantly decreased, aggression ratings did not significantly decrease.
Branford 1998 EC III	Paroxetine dose range 20-40mg Fluoxetine dose range 20-80mg	Aggression, perseveration of rituals	Retrospective Uncontrolled	33	CGI	Use of SSRIs indicated: 40% showed no benefit, 24% deteriorated and 36% had a reduction in perseverative and maladaptive behaviour.
Davanzo 1998 III	Paroxetine 35mg	Aggression, SIB	Prospective Uncontrolled	15	Observations of severity and frequency of target behaviours.	Only severity, not frequency of aggression reduced over the whole treatment period.

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, CGI: Clinical Global Impressions scale

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