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

Technical Document

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UNIVERSITY OF BIRMINGHAM
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Let Wisdom Guide
MENCAP
Understanding learning disability

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

Technical Document Section 3.6: Systematic Reviews: Opioid Antagonists

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MENCAP
Understanding learning disability

Opioid antagonists

Identification of primary trials on the use of opioid antagonists in the management of behaviour problems in adults with a learning disability.

Databases used

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

Search terms

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

85. exp naloxone/ or exp naltrexone/
86. (naltrexone or nalorex or naloxone or narcan).tw.
87. 85 or 86
88. 53 and 84 and 87
89. limit 88 to (human and ("300 adulthood <age 18 yrs and older>" or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs> or 360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 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	27	6	11
Medline	24	7	13
Embase	39	7	24
Cinahl	39	43	6

Selection process

Search 1:
A total of 129 citations were retrieved by the searches and a quick scan through these led to 100 exclusions based on duplication, title and abstract. 29 citations underwent criteria scrutiny of which 11 were put aside in a box due to criteria satisfaction but small sample size and the full text was required for 8.

A close examination of the 8 full texts indicated that a further 2 studies could be excluded; the reasons for excluding these are given in table 12. Another 2 studies were added to the box, again due to relevance but small sample size. The remaining 4 studies qualified for data extraction and quality assessment.

A breakdown of the selection process for this search is shown in figure 17.

Search 2:
63 citations were generated in this search including case series to controlled trials. All citations were examined to make sure that any relevant controlled trials would not be missed. With the exception of 2, all the other citations were undoubtedly eliminated from the search on the basis of duplication, title and abstract. 2 full texts were obtained for further inspection, however these too failed to meet the inclusion criteria and were thus excluded. The reasons for excluding these last 2 studies are given in table 12.

A breakdown of the selection process for this search is shown in figure 18.

Search 3:
All 54 citations that were retrieved in this search were scanned to make sure that no controlled trials would be overlooked. However, it was possible to exclude all of them based on duplication, title and abstract. Previous hand searching had yielded 3 citations for which decisions on whether to include or exclude them could not be made from their titles or abstracts. Therefore, the full texts of these 3 citations were attained.

The breakdown of the selection process for this search is shown in figure 19.

Results: Included studies

Search 1:
On the whole, 4 studies fulfilled the inclusion criteria for this search.

All the studies recognised for inclusion in this review were concerned with the effectiveness of the opioid antagonist naltrexone in the management of behaviour problems in adults with a learning disability. Three of the studies were prospective trials (Sandman *et al*, 2000; Willemsen-Swinkells *et al*, 1995; Sandman *et al*, 1993) and one was a retrospective case series study (Casner *et al*, 1996). Willemsen-Swinkells *et al* 1995 was the only proper RCT identified. The characteristics of these studies are provided in table 13.

Search 2 yielded no additional papers.

Search 3:
Eventually it was accepted that only one of the three full texts that were examined met the inclusion criteria from this search. The reason for excluding the other two are given in table 12.

The included study investigated the effects of naltrexone on aggression in a population of children with both a learning disability and a diagnosis of autistic disorder (Campbell *et al*, 1993). The characteristics of this study are given in table 14.

An overall summary of the findings for these 3 searches are shown in figure 20.

Figure 17: Search 1 – Opioid Antagonists

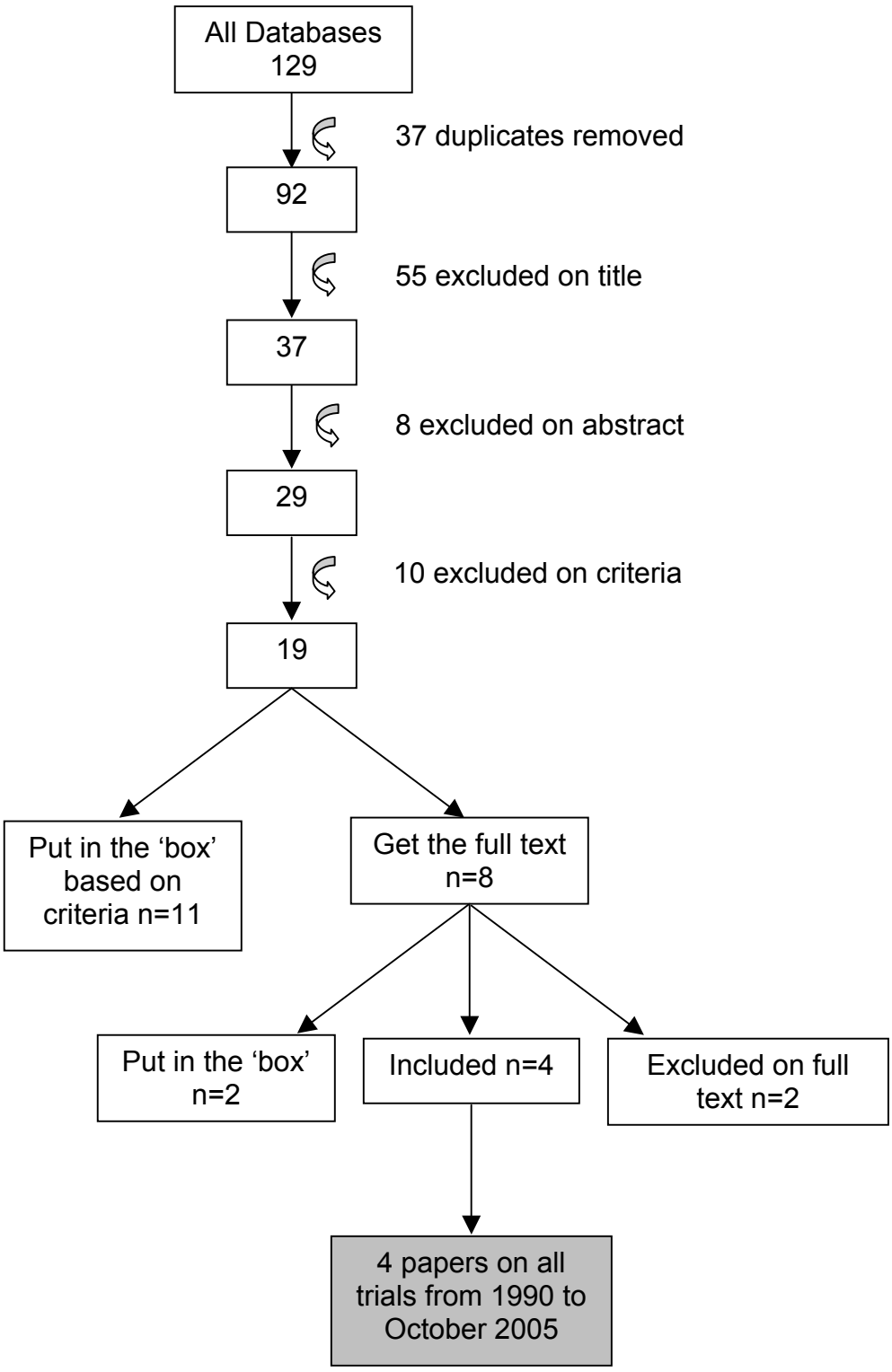


Figure 18: Search 2 - Opioid Antagonists

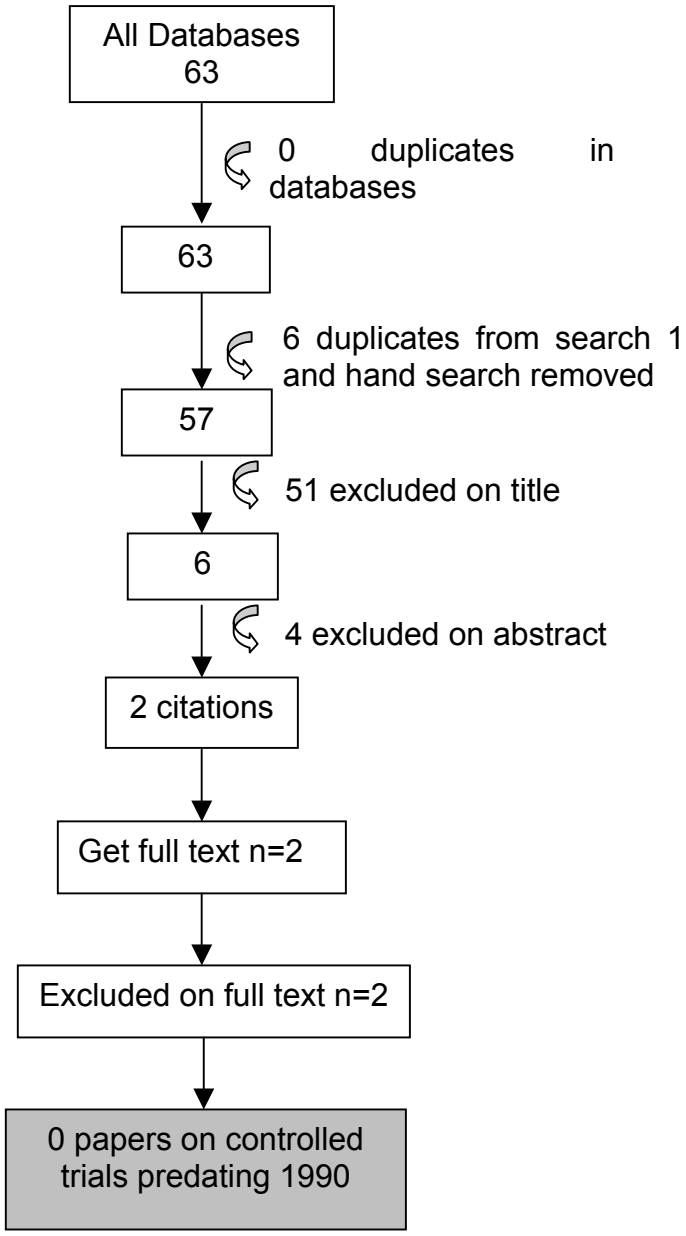


Figure 19: Search 3 - Opioid Antagonists

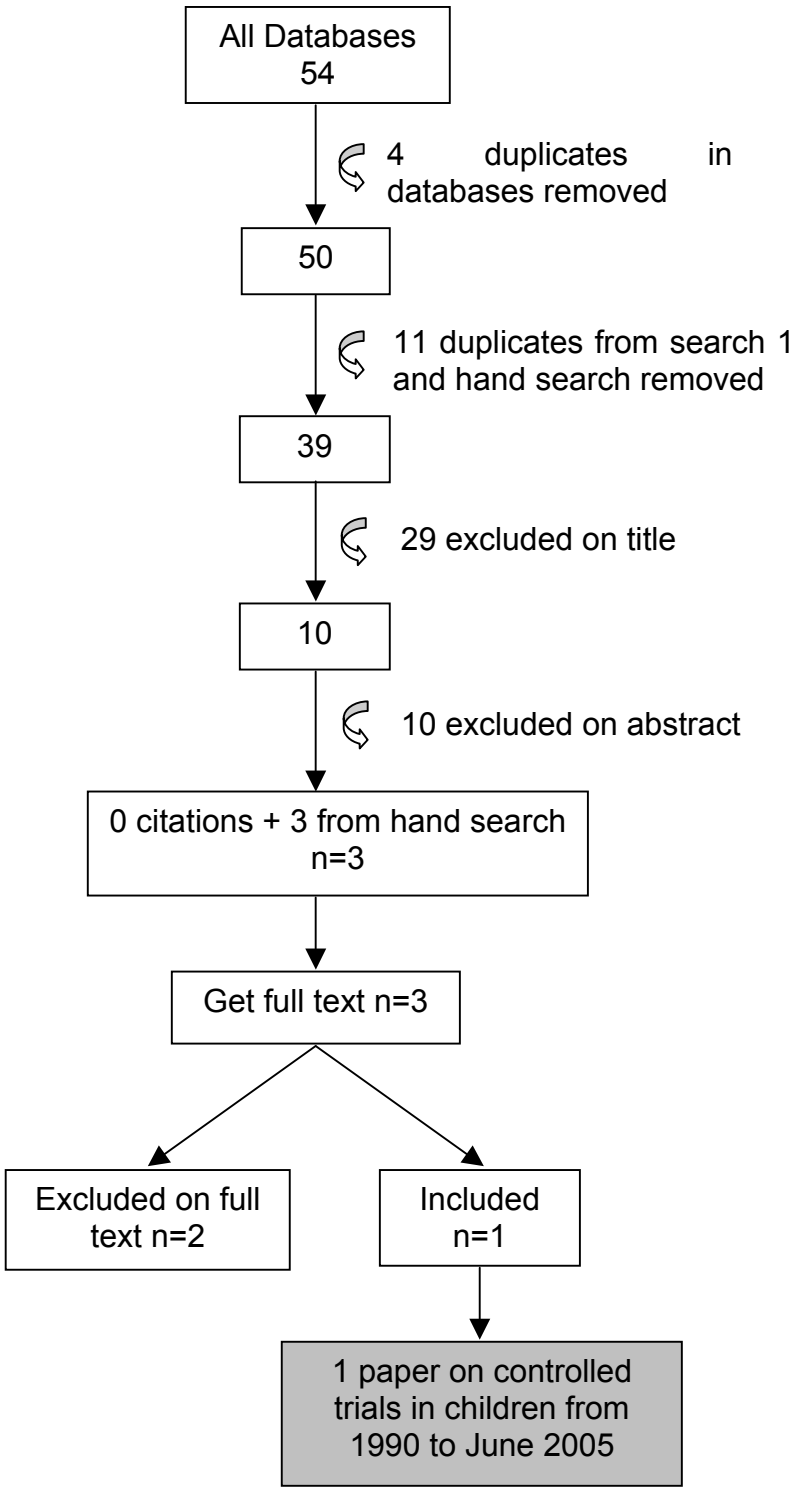
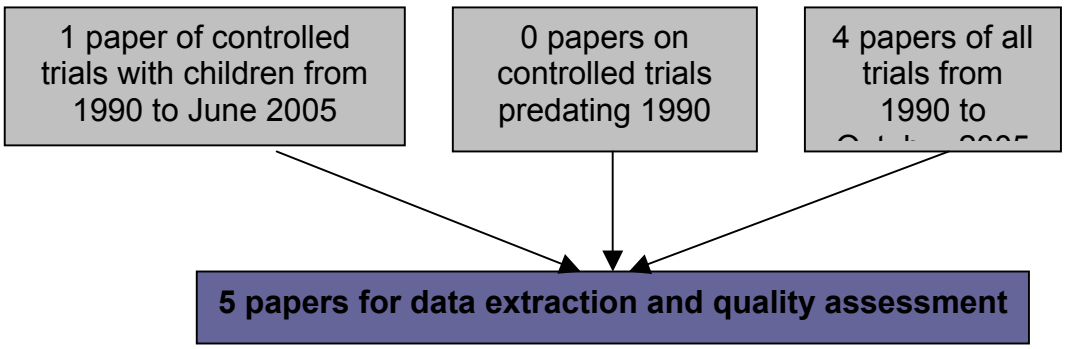


Figure 20: Summary of the opioid antagonists search



Opioid Antagonists Review: Summaries of included studies

Controlled trials

Adults

Sandman et al. (1993)

Participants
24 participants but 21 completed study. Age range for the adults was 20-67 years, including 1 child of 13 years (75% males). 50% had a profound LD, 33% severe and 4% moderate. 42% had co-morbid epilepsy. All presented with self-injurious behaviour that had been unsuccessfully treated with physical restraints, psychoactive medications and behavioural techniques in the past.

Intervention
Naltrexone was administered in different doses of 0.5, 1.0 and 2.0 mg/kg for 3 weeks each.

Method
Although described as a RCT with a double blind, placebo-controlled design, this study cannot be regarded as such because no comparison has been made between treatment and placebo. Instead, comparisons have been made among the differing dosages that were administered to the participants. There were 2 weeks of open placebo followed by 8 weeks of double blind treatment with the differing doses of naltrexone. Placebo intervened each of the medication phases.

Follow-up
Participants were examined over a continuous 10-week period.

Outcomes
1. Approximately 20 hours of weekly direct observations per participant were videotaped with computerised direct assessment of the frequency, duration and severity of SIB and stereotypy. 2. The Objective Neurological Examination (ONE) was developed for this study. 3. An adapted version of Conners' Parent-Teacher Questionnaire. 4. Summation of Maladaptive Expression (SOME) rating scale was developed for this study to measure behaviour change. 5. Fairview Adaptive Individualised Record (FAIR) assessing activities of daily living. 6. Dyskinesia Identification System-Condensed User Scale (DISCUS) and the Berkson and Davenport (1962) stereotypies checklist (BDC).

Results
Naltrexone was effective in reducing SIB by 50% in significant numbers at the dose of 2mg/kg in 11/21 (52%; $p<0.01$). Doses of 0.5mg/kg and 1mg/kg were

less effective with improvements seen in 4/21 (19%) and 3/21 (14%) respectively. Overall, 18/21 (86%) of the participants had a 25% reduction in SIB after a single dose of naltrexone ($p<0.0001$). There were no major side effects noted.

Comments
This study shows improvement of SIB in the short term with a higher dose of naltrexone, although the numbers are too small to arrive at any valid conclusions. There was no separate control group for comparison, and the follow-up duration was inadequate. This study scored 6/9 on quality assessment.

Sandman et al. (2000): a follow-up study of Sandman et al (1993) looking into the long-term effects of naltrexone intervention.

Participants
15/21 participants from an earlier study (Sandman et al, 1993) were recruited. Only 1 child of 13 years was included and the rest of the sample were adults, thus the age range was 13-50 years (67% male). 12 (80%) had a profound LD, 2 (13%) severe and 1 (7%) moderate. Co-morbid disorders of epilepsy, Tourette syndrome, aortic stenosis and cardiomyopathy were present. The target behaviour was self-injury.

Intervention
Naltrexone single most effective dose of 0.5, 1.0 or 2.0 mg/kg.

Method
A double blind, multiple baseline, prospective study. No comparison between treatment versus placebo. The length of time on naltrexone was initially 8 weeks and then up to 3 months.

Follow-up
Participants were followed-up weekly for 18 months.

Outcomes
15 minutes of weekly direct observations were videotaped with computerised direct assessment for frequency and duration of SIB.

Results
A subgroup of patients showed a decrease of SIB for 1 year without treatment after acute exposure to naltrexone. Five subjects who showed decrease of SIB by 70% then showed increase of SIB after long-term treatment with naltrexone. Those in whom SIB increased after 1-year treatment hiatus, showed a decrease in SIB after their first exposure to long-term treatment.
In the present arm of this study, a reduction of at least 25% in SIB was found in 4/15 (27%) participants and a reduction of at least 50% in 6/15 (40%; $p<0.01$) during the first 3 months of treatment. In the second 3-months phase, a reduction in SIB was apparent in 8/12 (67%) and 5/8 of these participants maintained at least a 25% improvement in SIB.

Comments
This study provides results for the long-term effects of naltrexone intervention in the present context. However, outcomes and results are quite difficult to interpret and the sample size was very small. Furthermore, no separate control group has been included for comparison. This study achieved 9/14 on quality assessment.

Willemsen-Swinkels et al. (1995)

Participants
33 adults, age range 18-46 years (82% male). All participants had a profound to mild LD. There were 3 groups presenting with – autism and SIB, autism only and SIB only. 5 had co-morbid epilepsy.

Intervention
Initially all participants were given naltrexone hydrochloride 100mg/d. Then 19 (58%) were treated with 50mg/d and 14 (42%) with 150mg/d of naltrexone hydrochloride for 4 weeks.

Method
A randomised, double blind, placebo-controlled trial with a crossover design.

Follow-up
The medication treatment period lasted for 4 weeks and it appears that the overall trial period was 15 weeks.

Outcomes
1. ABC.
2. . CGI.
3. Scores on a 5-point scale checklist of target behaviours.
4. Some participants (n=11) were also subjected to direct observation.
5. Side effects were considered by direct questioning of staff and participants on completion of the trial.

Results
The first cohort (50mg dose) demonstrated no effect with naltrexone and the second cohort (150mg dose) too showed no effect on SIB but did demonstrate worsening of stereotypical behaviour. Scores on the CGI suggested placebo effect to be better than naltrexone ($p=0.03$).

Comments
This study presented negative findings in that naltrexone was found to be ineffective. The problems with this study are that it has broad aims, SIB symptoms were inadequately measured and there was direct observation for only some of the participants. The target symptom checklist was not validated and finally the dose of naltrexone was kept low. Thus, it was difficult to draw any valid conclusions from this study. This study scored 7/14 on quality assessment (3/5 on Jadad criteria).

Children

Campbell et al. (1993)

Participants
41 inpatient children, age range 2.9-7.8 years (83% male). All participants had a DSM-III-R diagnosis of autistic disorder with infantile onset; 84% had a mild to severe LD and 16% borderline IQ or at dull-normal level. The target behaviour was aggression.

Intervention
Naltrexone 1mg/kg per day or a matching placebo. Treatment duration for both groups was 3 weeks.

Method
A randomised, double blind, placebo controlled study. Following a 2-week washout period and a 2-week baseline period where all participants received placebo, the participants were randomly assigned to receive either naltrexone (n=23) or placebo (n=18) with a final 1-week post treatment placebo period.

Follow-up
The participants were assessed for behaviour 4 times during the study, twice during the placebo baseline, at the end of the 3-week treatment phase and the end of the post treatment placebo period. Overall, the trial lasted for a period of 6 weeks.

Outcomes
Two independent child psychiatrists, a nurse and teachers made the outcome assessments. 1. Clinical Global Impressions (CGI) scale and Nurses Global Impressions (NGI) scale were combined to give Global Clinical Consensus (GCC) ratings. 2. The Aggression Rating Scale measured aggression to self and others; an instrument developed by the researchers for use in their clinics that rates severity on a 7-point scale. 3. Side effects were measured using the naltrexone side-effect checklist.

Results
On the GCC ratings, no participant was rated as worse when compared to baseline; also no association between medication status and improvement was found ($p=0.35$). However, the proportion of children rated moderately to markedly improved was 39.9% for placebo and 56.5% for naltrexone. The CGI severity scores also demonstrated no significant differences between the two groups. Similarly, on the Aggression Rating Scale no significant main effects for medication when compared to placebo were observed for either self-injurious behaviour or aggression to others.

Comments
The results indicate that naltrexone was not superior to placebo in the treatment of aggression. However, the treatment phase only lasted three

weeks, which may not have provided enough time for treatment effects to be established. There was no explanation of the randomisation and blinding methods employed. In addition, there was no breakdown of the demographic details for each group - only combined statistics, and the Aggression Rating Scale is not an instrument that has been reliably validated. This study scored 7/14 on quality assessment (4/5 on Jadad criteria).

Retrospective studies

Casner et al. (1996)

Participants
56 adults, average age 35.3 (SD ± 9.7) years (55% male). 80% had a severe to profound LD. Co-morbid disorders included epilepsy, pervasive developmental disorder, organic/affective disorder and autism. The target behaviour was self-injurious behaviour.

Intervention
Naltrexone 25-300 mg/day (average dose 96.8mg/day) for 3-87 months (36.5 +/- 19.5).

Method
A retrospective review of participants displaying SIB whom had been treated with naltrexone over a 5-year period.

Follow-up
Outcomes were measured 3–87 months after treatment from case note records.

Outcomes
Data was collected from case notes. Recorded rate of SIB in notes with at least 50% reduction achieved was used to define the participants as 'objective responders'. This was determined by one of the investigators whom reviewed the behavioural data.

Results
32/56 (57%) were classified as 'responders' and 1 experienced side effects. Blind review of SIB records showed a 50% reduction in 13 (25%) participants. All 13 had a severe/ profound learning disability, whilst 12 non-responders had a mild learning disability.

Comments
No valid conclusions can be drawn from this study as it has significant methodological problems. The definition for the outcome lacks clarity and there was no control group or statistical analysis reported in support of the results. The study is retrospective in design, however represents natural clinical settings with inclusion of the whole population and had a long duration of follow up. This study scored 4/9 on quality assessment.

Table 12: Studies excluded on full text

Study	Summary	Reason for exclusion
Kolmen, 1995	This was a RCT investigating the efficacy of naltrexone in 13 children with autistic disorder. Parent and teacher ratings showed a trend towards improvements in areas of restlessness and initiation of communication. Overall, 8/13 children were considered as responders to naltrexone.	The study concentrated on treating symptoms of autism rather than a behaviour problem per se. Thus, there was lack of outcome data relating to behaviour.
Kyriakides, 1980	This was a RCT in 3 participants with Prader Willi Syndrome. Naloxone was given to observe its effects on food intake. Food intake was reduced in 2/3 participants.	There were less than ten participants in the study.
Raymond, 2002	This article presented two case studies of adults with compulsive sexual behaviour. Treatment with naltrexone proved successful with a dramatic decrease in symptoms.	The two participants in the study did not have a LD.
Szymanski, 1987	This was a RCT of the treatment of self-injurious behaviour with naltrexone in participants with a LD. There were no therapeutic effects observed with naltrexone treatment.	There were less than ten participants in the study.
Tsiouris, 2003	This was an open trial assessing whether psychotropic medication treatment of a previously undiagnosed psychiatric disorder would reduce the incidence of SIB. It was suggested that SIB in 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 intervention included in the study. The intervention was the diagnosis of an underlying psychiatric disorder and then this was treated appropriately.
Willemsen-Swinkells, 1995	This was a placebo-controlled trial of naltrexone in 23 autistic children. A single dose of naltrexone did not have any beneficial effects on social behaviour, but did affect levels of activity and attention.	Some of the children had IQ scores of greater than 70, and there was no separate data for these or for those whom had a LD.

Table 13: Studies included in the opioid antagonists review: Adults

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Sandman 2000 EC III	Naltrexone Single dose 0.5, 1.0 or 2.0mg/kg	SIB	*Double blind, prospective (follow-up of Sandman, 1993 below)	15 (including 1 under 18 years of age)	Direct observations	Subgroup of participants showed a decrease in SIB for 1 year after acute exposure to naltrexone. 5 showed an increase in SIB after long-term treatment.
Casner 1996 EC III	Naltrexone 96.8mg	SIB	Retrospective Uncontrolled	56	Retrospective review of behavioural data	57% responded to naltrexone. Blind review showed a 50% reduction in SIB in 25% of participants.
Willemsen-Swinkells 1995 EC I	Naltrexone n=19: 50mg n=14: 150mg	SIB	RCT Crossover	33	ABC, CGI, target symptom checklist, some had direct observations	No therapeutic effect with naltrexone.
Sandman 1993 EC III	Naltrexone doses of 0.5, 1.0 and 2.0mg/kg	SIB	*Prospective trial	24 (including 1 under 18 years of age)	Direct observations, ONE, adapted version of Conners' Parent-Teacher Questionnaire, SOME rating scale, DISCUS, Berkson & Davenport (1962) Stereotypies Checklist (BDC)	Naltrexone decreased SIB by 50% at a dose of 2mg/kg in 52% of participants. Single dose effect of at least a 25% reduction was apparent in 86%.

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, ONE: Objective Neurological Examination, SOME: Summation of Maladaptive Expression, DISCUS; Dyskinesia Identification System – Condensed User Scale

*No comparison was made between treatment versus placebo and hence, these trials cannot be allocated an evidence category rating of II or I.

Table 14: Studies included in the opioid antagonists review: Children

Author/ **Evidence category (EC)**	**Drug/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Campbell 1993 EC I	Naltrexone 1mg/kg	Aggression	RCT	Study group: 23, controls: 18	CGI and NGI combined to give Global Clinical Consensus (GCC), Aggression Rating Scale, Naltrexone Side Effects Checklist	No therapeutic effect with naltrexone.

Evidence Categories - I: randomised controlled trial (RCT), CGI: Clinical Global Impressions, N

References for search 1

Included studies (N>10)

1. Casner JA, Weinheimer B & Gualtieri CT. Naltrexone and self-injurious behavior: A retrospective population study. *Journal of Clinical Psychopharmacology* 1996; 16 (5): 389-394.
2. Sandman CA, Hetrick W, Taylor DV, Marion SD, Touchette P, Barron JL, Martinezzi V, Steinberg RM & Crinella FM. Long-term effects of naltrexone on self-injurious behavior. *American Journal on Mental Retardation* 2000; 105 (2): 103-117.
3. Sandman CA, Hetrick WP, Taylor DV, Barron JL, Touchette P, Lott I, Crinella F & Martinezzi V. Naltrexone reduces self-injury and improves learning. *Experimental and Clinical Psychopharmacology* 1993; 1 (1-4): 242-258.
4. Willemsen-Swinkels SHN, Buitelaar JK, Nijhof GJ & Van Engeland H. Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults: Double-blind placebo-controlled studies. *Archives of General Psychiatry* 1995; 52 (9): 766-773.

Relevant studies (N<10)

1. Benjamin S, Seek A, Tresise L, Price E & Gagnon M. Case study: Paradoxical response to naltrexone treatment of self-injurious behavior. *Journal of the American Academy of Child & Adolescent Psychiatry* 1995; 34 (2): 238-242.
2. Bodfish JW, McCuller WR, Madison JM, Register M, Mailman RB & Lewis MH. Placebo, double-blind evaluation of long-term naltrexone treatment effects for adults with mental retardation and self-injury. *Journal of Developmental & Physical Disabilities* 1997; 9 (2): 135-152.
3. Buzan RD, Dubovsky SL, Treadway JT & Thomas M. Opiate antagonists for recurrent self-injurious behavior in three mentally retarded adults. *Psychiatric Services* 1995; 46 (5): 511-512.
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9. Sandman CA, Barron JL & Colman H. An orally administered opiate blocker, naltrexone, attenuates self-injurious behavior. *American Journal on Mental Retardation* 1990; 95 (1): 93-102.
10. Smith SG, Gupta KK & Smith SH. Effects of naltrexone on self-injury, stereotypy, and social behavior of adults with developmental disabilities. *Journal of Developmental & Physical Disabilities* 1995; 7 (2): 137-146.
11. Symons FJ, Tapp J, Wulfsberg A, Sutton KA, Heeth WL & Bodfish JW. Sequential analysis of the effects of naltrexone on the environmental mediation of self-injurious behavior. *Experimental & Clinical Psychopharmacology* 2001; 9 (3): 269-276.
12. Taylor DV, Hetrick WP, Neri CL, Touchette P, Barron JL & Sandman CA. Effect of naltrexone upon self-injurious behavior, learning and activity: A case study. *Pharmacology, Biochemistry & Behavior* 1991; 40 (1): 79-82.
13. Thompson T, Hackenberg T, Cerutti D, Baker D & Axtell S. Opioid antagonist effects on self-injury in adults with mental retardation: Response form and location as determinants of medication effects. *American Journal on Mental Retardation* 1994; 99 (1): 85-102.

Excluded studies

1. Barrera FJ, Teodoro JM, Selmeci T & Madappuli A. Self-injury, pain, and the endorphin theory. *Journal of Developmental & Physical Disabilities* 1994; 6 (2): 169-192.
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12. Xeniditis K, Russell A & Murphy D. Management of people with challenging behaviour. *Advances in Psychiatric Treatment* 2001; 7 (2): 109-116.

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Excluded studies

1. Kyriakides M, Silverstone T, Jeffcoate W & Laurence B. Effect of naloxone on hyperphagia in Prader-Willi syndrome. *Lancet* 1980; 1(8173): 876-7.
2. Szymanski L, Kedesdy J, Sulkes S & Culter A. Naltrexone in treatment of self-injurious behaviour: A clinical study. *Research in Developmental Disabilities* 1987; 8: 179-190.

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Included studies

1. Campbell M, Anderson LT, Small AM, Adams P, Gonzalez NM & Ernst M. Naltrexone in autistic children: behavioural symptoms and attentional learning. *Journal of the American Academy of Child and Adolescent Psychiatry* 1993; 32 (6): 1283-1291.

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Excluded studies

1. Kolmen BK, Feldman HM, Handen BL & Janosky JE. Naltrexone in young autistic children: A double-blind, placebo-controlled crossover study. *Journal of the American Academy of Child and Adolescent Psychiatry* 1995; 34 (2): 223-231.
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