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Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: a systematic review

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Abstract

Background ASC (autism spectrum conditions) may result from a failure of striatal beta endorphins to diminish with maturation. Many symptoms of ASC resemble behaviours induced in animals or humans by opiate administration, including decreased socialisation, diminished crying, repetitive stereotypies, insensitivity to pain and motor hyperactivity. Naltrexone, an opioid antagonist, has been used in the management of children with ASC and can produce a clinically significant reduction in the serious and life-threatening behaviour of self-injury for individuals who have not been responsive to any other type of treatment and is important for this reason. It was therefore appropriate to reconsider the available evidence and a systematic review was undertaken.

Methods Four electronic databases were searched for relevant journal articles. In addition, cross-referencing of pertinent reviews and a hand search for articles in major international intellectual disability (ID) journals between the years 2010 and 2012 was carried out to ensure that all relevant articles were identified. We also searched databases for unpublished clinical trials to overcome publication bias. Each database was searched up to present (February 2013) with no restrictions on the date of publication. The search terms consisted of broad expressions used to describe ID and autistic spectrum disorder as well as terms relating to opioid antagonists and specific drugs. All studies identified by the electronic database search and hand search were examined on the basis of title alone for relevance and duplication. The abstracts of the remaining papers were then scrutinised against the inclusion criteria. Where abstracts failed to provide adequate information, the full texts for these papers

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were obtained. All the full texts were then evaluated against the inclusion proforma. Two reviewers carried out all the stages of the process independently. The reviewers met to discuss their selections and where disagreements arose, these were settled by discussion with a member of the study group. Data from each study meeting the inclusion criteria were extracted on a pre-piloted data extraction form. The quality of each study was further assessed using the Jadad scale, a tool developed to assess the quality of randomised controlled trials.
Results 155 children participated in 10 studies; 27 received placebo. Of the 128 that received naltrexone 98 (77%) showed statistically significant improvement in symptoms of irritability and hyperactivity. Side effects were mild and the drug was generally well tolerated.
Conclusions Naltrexone may improve hyperactivity and restlessness in children with autism but there was not sufficient evidence that it had an impact on core features of autism in majority of the participants. It is likely that a subgroup of children with autism and abnormal endorphin levels may respond to naltrexone and identifying the characteristics of these children must become a priority.

Keywords autism, children, hyperactivity, intellectual disability, naltrexone, opioid antagonists

Introduction

The reported prevalence of autism spectrum conditions (ASC) in children varies from 110 per 10 000 (Kogan *et al.* 2009) in parent reported studies to 157 per 10 000 in school population-based studies (Baron-Cohen *et al.* 2009) in the UK and 11.3 per 1000 (Autism and Developmental Disabilities Monitoring Network Surveillance 2012) based on information from children's evaluations records in the USA. ASC may represent the final expression of various aetiological factors including genetic events (e.g. tuberous sclerosis), metabolic diseases (e.g. phenylketonuria), infectious diseases (e.g. rubella) or structural abnormalities (e.g. mild hydrocephalus). Other aetiological factors include subtle neuroanatomical and or biochemical abnormalities in the brain that somehow result in ASC (Chamberlain & Herman 1990). Panksepp (1979) proposed that ASC may result from a failure of striatal beta endorphins to diminish with maturation. Many symptoms of ASC resemble behaviours induced in animals or humans by opiate administration, including decreased socialisation, diminished crying, repetitive stereotypies, insensitivity to pain and motor hyperactivity (Feldman *et al.* 1999). In at least a subgroup of individuals with ASC, there may be a dysfunction in the pineal–hypothalamic–pituitary–adrenal axis which modulates propiomelanocortin peptides and serotonin leading to over secretion of opioid peptides and brain serotonin (Sandman 1988; Chamberlain & Herman 1990). Naltrexone, an opioid antagonist, has been used in the management of children with ASC. Elchaar *et al.* (2006) reviewed the safety and efficacy of naltrexone in paediatric patients with ASC by examining 25 studies (3 case reports, 8 case series and 14 clinical studies) from 1966 to 2006. Their conclusion was that naltrexone was effective in attenuating hyperactivity, agitation, irritability, temper tantrums, social withdrawal and stereotyped behaviour. Participants may also have experienced improved attention and eye contact after treatment. This suggests that a subgroup of children with ASC may have abnormalities in endogenous opioid system.

Children with ASC may display problem behaviours (PB) for which there may be many reasons. Repetitive stereotyped patterns of behaviours may include self-injurious behaviours (SIB). Twenty-five experts invited by the National Institute of Child Health and Human Development (NICHD) to discuss the relations among the genetic, neurobiological and behavioural causes and treatments for SIB proposed two distinct patterns. One pattern consists of bouts that are most likely maintained by environmental contingencies (Schroeder *et al.* 2002). The second pattern involves protracted periods of SIB that are most likely under the primary influence of biological factors. Environmental theories include the balance between arousal and homeostasis (Baumeister & Forehand 1973) where SIB may block out excessive stimulation or increase arousal during periods of under stimulation. SIB may also have learning, social and communicative functions (Schroeder *et al.* 2002).

Biological factors may include underlying anxiety or a mood disorder, seizure activity or a psychotic illness. Anxiolytics, antidepressant, mood stabiliser

and anticonvulsant medications can all be used appropriately if the cause of self-injury is established (Unwin & Deb 2011). Opioid antagonists have also been used in the treatment of SIB. Sandman & Kemp (2011) have summarised the rationale behind this by pointing out that some individuals who self injure repeatedly appear to be immune to pain; they overcome interventions designed to reduce self-injury in a manner consistent with seeking positive reward. Many medications which reduce pain or induce pleasure are addicting. According to the addiction hypothesis (Sandman & Hetrick 1995), opioid mechanisms are involved in the maintenance of high frequencies of SIB. In Pain Hypothesis, self-injury does not cause pain because excessive basal activity has induced an opioid analgesic state and with the experience of pain reduced, individuals inflict self harm as a form of stimulation. On the other hand addiction hypothesis suggests that self-injury or more generally stereotypic behaviour stimulates production and release of endogenous endorphins; therefore, chronic maintenance of these behaviours is due to either addiction to endogenous opiate like substances or possible reinforcement brought about by a central release of endorphins that is contingent on behaviour.

There has been support for the hypothesis that the opioid system may be abnormal in some people displaying SIB from reviews by Symons *et al.* (2004), Elchaar *et al.* (2006) and Sandman & Kemp (2011). Symons *et al.* (2004) found that 80% of subjects improved relative to baseline during naltrexone administration and in 47% of subjects SIB was reduced by 50% or greater. They found that males were more likely than females to respond and there was no significant relationship between treatment outcomes and autism status or form of self-injury. On the other hand, Elchaar *et al.* (2006) report that naltrexone was generally effective in decreasing self-injury in paediatric patients with autistic disorder.

Sandman & Kemp (2011) conclude that naltrexone produces a clinically significant reduction in the serious and life-threatening behaviour of self-injury for individuals who have not been responsive to any other type of treatment and is important for this reason. They point out that these results with naltrexone are important for a second reason because they suggest that a specific biological system may be disregulated in a subgroup of patients.

Disregulated opioid system may cause both features of ASC and self-injury in some individuals with ASC. While Symons *et al.* (2004) did not find a significant treatment outcome with naltrexone between autism status and SIB, Elchaar *et al.* (2006) found that SIB reduced with naltrexone in children with autism. In the recent years, naltrexone does not appear to be used in the treatment of SIB. Sandman & Kemp (2011) make a strong case for reconsidering naltrexone. It is therefore appropriate to reconsider the available evidence and a systematic review was undertaken.

Methods

Search strategy

Four electronic databases, namely Psychinfo, MEDLINE, Cochrane and Embase, were searched for relevant journal articles. In addition, cross-referencing of pertinent reviews and a hand search for articles in *Journal of Intellectual Disability Research*, *Journal of Intellectual Disability*, *American Journal of Intellectual and Developmental Disability*, *Research in Developmental Disability*, *Journal of Applied Research in Intellectual Disability* and *Journal of Autism and Developmental Disorders* between the years 2010 and 2012 was carried out to ensure that all relevant articles were identified. We also searched http://www.clinicaltrials.gov, http://www.clinicaltrialsregister.eu, http://www.controlled-trials.com, and http://www.public.ukcrn.org.uk for unpublished clinical trials to overcome publication bias. Each database was searched up to present (February 2013) with no restrictions on the date of publication.

The search terms consisted of broad expressions used to describe ID and autistic spectrum disorder as well as terms relating to opioid antagonists and specific drugs.

The search terms for intellectual disability were:

learning disab* (truncated to include disabled, disability, disabilities)
intellectual* disab* (truncated to include intellectual, intellectually, disabled, disability, disabilities)
intellectual* impair* (truncated to include intellectual, intellectually, impairment, impaired)

development* disab* (truncated to include development, developmental, developmentally, disabled, disability, disabilities)
development* impair* (truncated to include development, developmental, developmentally, impair, impairment, impaired)
mental* retard* (truncated to include mental, mentally, retardation, retarded)
mental* challenged (truncated to include mental, mentally)
mental* handicap* (truncated to include mental, mentally, handicap, handicapped)
mental* impair* (truncated to include mental, mentally, impairment, impaired)
mental* deficien* (truncated to include mental, mentally, deficient, deficiency)

Subaverage intelligence

The search terms for autism spectrum disorders were:

Autis* (truncated to include autism, autistic)
Autis* spectrum disorder* (truncated to include autistic, autism, disorder, disorders, disordered)
Autis* spectrum condition* (truncated to include autistic, autism, condition, conditions)
Asperger* (truncated to include Asperger, Aspergers, Asperger's, Aspergoid, Aspergers syndrome)
Infant* Autis* (truncated to include infant, infantile, autism, autistic)
Child* Autis* (truncated to include children, childhood, autistic, autism)
Pervasive* development* disorder* (truncate to include pervasive, pervasively, development, developmental, developmentally, disorder, disorders, disordered)
Autis* Psychopath* (truncated to include autistic, autism, psychopath, psycopathy, psychopathies)
AS* (truncated to include AS, ASD, ASC)
PDD
Kanner* Syndrome (truncated to include Kanner, Kanners, Kanner's)
Atypical* Autis* (truncated to include atypical, atypically, autism, autistic)

The search terms for opioid antagonists were:

Nal* (truncated to include naloxone, nalorex, naltrexone, nalone)
Nar* (truncated to include narcan, narcanti)
Opioid* antagonist* (truncated to include opioid, opioids, antagonists, antagonist)

Inclusion criteria

Criteria for selecting studies for inclusion in the review were devised and piloted prior to the commencement of the search. The inclusion criteria for the review were as follows:

Types of studies: Only randomised controlled trials were included.
Types of participants: Participants could be children and adults of any age with ID (as defined by the author or IQ below 70) and exhibiting PB (as defined by the author). Studies with participants both with and without intellectual disability (ID) were included only if separate data for the individuals with ID were available. Participants with and without autism spectrum disorder were included. Dementia was an exclusion criterion.
Sample size: Studies with one or two participants were excluded.
Target symptom: There were no restrictions on symptom – could be a behavioural problem or symptoms relating to ASC.
Types of interventions: As this review was to help clinical practice, Naloxone was excluded as it is short acting and has to be administered parenterally. Any opioid antagonist given by mouth, prescribed for the management of PB was included. Concurrent use of psychotropic medications was not an exclusion criterion.
Types of outcome measures: Outcome measure could be any relating to pre and post intervention including behavioural measures and measures of side effects.
Language: Only English language papers were included.
Publication criteria: There was no restriction on type or year of publication and could include book chapters and conference proceedings.

Selection process

A proforma setting out the inclusion criteria was developed and piloted by two reviewers (AR and AR). To begin with, all studies identified by the electronic database search and hand search were

examined on the basis of title alone, which allowed for the exclusion of those that were clearly irrelevant or duplicated. The abstracts of the remaining papers were then scrutinised against the inclusion criteria by two reviewers, which allowed for the removal of further papers. Where abstracts failed to provide adequate information, the full texts for these papers were obtained. All the full texts were then evaluated against the inclusion proforma. Two reviewers (AR and AR) carried out all the stages of the process independently. The reviewers met to discuss their selections and where disagreements arose, these were settled by discussion with a member of the study group (SD). Data from each study meeting the inclusion criteria were extracted on a pre-piloted data extraction form.

It became evident that there were clear differences between RCTs where children were participants compared with those involving adults. The RCTs on adults focused primarily on self-injury while those involving children primarily focused on ASC. In addition there are different clinical, practical, legal and ethical issues in the psychopaharmacotherapy. This paper will review RCTs involving children.

The quality of each RCT was assessed using the Jadad criteria, a standardised tool developed to assess the quality of RCTs (Jadad *et al.* 1996). The trials can be scored on the basis of Randomisation (maximum score of 2 on the basis of the whether randomisation was appropriate, a point reduced if not appropriate), Blinding (up to a maximum of 2 points or deduction as in Randomisation) and whether the fate of all patients is known, if not the reason for it. The main advantages of this scale are that it is easy to use, it contains many of the important elements that have empirically been shown to correlate with bias and it has known reliability and external validity.

Results

The databases generated 866 citations. A total of 712 were excluded on title and being duplicates. Out of the remaining 154, 78 were excluded on abstracts and 56 on studying the full text. The remaining 20 studies included 10 where the subjects were children and 10 where the subjects were predominantly adults (see Fig. 1).

Design

The 10 RCTs are summarised on Tables 1 and 2. 8 had a crossover design while two were parallel (Campbell *et al.* 1990, 1993).

Setting

Seven trials were conducted on outpatients (Leboyer *et al.* 1992; Bouvard *et al.* 1995; Kolmen *et al.* 1995, 1997; Willemsen-Swinkels *et al.* 1995, 1996; Williams *et al.* 2001). A third of the participants were outpatients in the Scifo *et al.*'s (1991) trial and all were inpatients in Campbell *et al.*'s (1990) and Campbell *et al.*'s (1993) trials.

Participants

Altogether 155 participants were studied among the 10 included studies. A total of 128 subjects received active treatment while 27 received placebo only in the two studies with parallel design (Campbell *et al.* 1990, 1993). The number of participants varied from four in Leboyer *et al.*'s (1992) study to 41 in Campbell *et al.*'s (1993) study. Williams *et al.*'s (2001) study included eight participants. The remaining studies included 10 or more participants. All the children had a diagnosis of ASC.

The level of ID was not stated in Bouvard *et al.*'s (1995) study; of the 10 participants, six were described as being non-verbal. In Campbell *et al.*'s (1990) study, the level of ability ranged from profound to borderline ID. In Campbell *et al.*'s (1993) study, the level of ability was available for 37 participants of whom eight had severe, nine moderate, 14 mild and five borderline ID and one child was described as being dull normal. The 13 children in Kolmen *et al.*'s (1995) study had a DQ between 21 and 115 with nine showing a DQ below 70. In Kolmen *et al.*'s (1997) study the mean DQ among the participants was 55. All the participants had severe ID in Leboyer *et al.*'s (1992) study. The participants in Scifo *et al.*'s (1991) study were all non-verbal except two and one had verbal language at a good cognitive level. It is unclear whether this child did not have ID The cognitive ability of the participants was not stated in Williams *et al.*'s (2001) study. Willemsen-Swinkels *et al.* (1995, 1996) studied the same group of children on two separate occasions, and the DQ was below 40 in

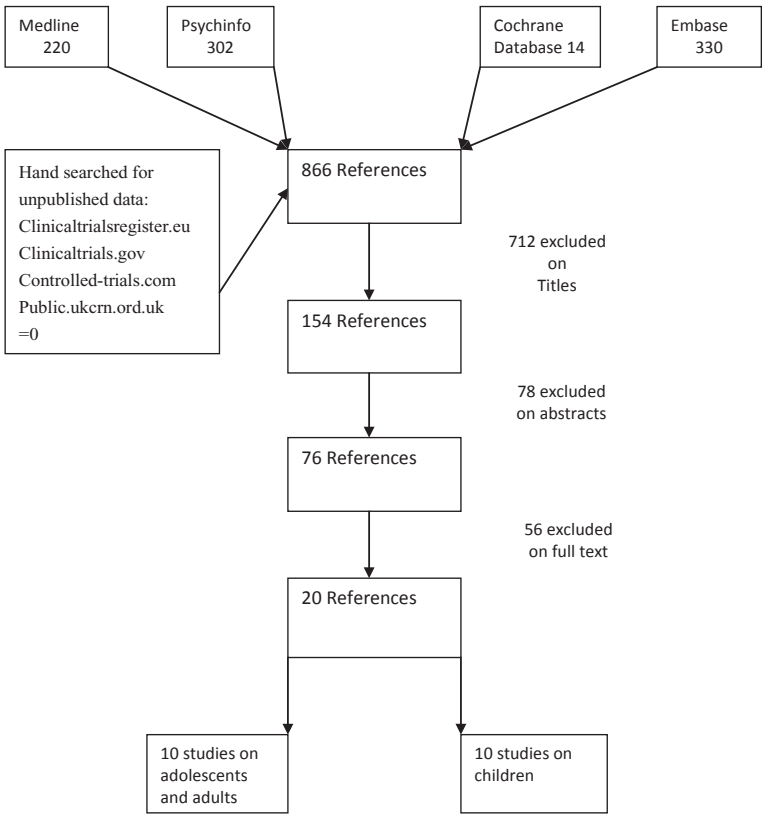

Figure 1 Selection process for citations.

four participants, between 40 and 55 in two, and between 55 and 70 in four participants while the others had a verbal quotient between 64 and 104. The participants were all boys in Williams *et al.*'s (2001) study; all the other studies included both boys and girls albeit the number of girls included was much smaller than boys (see Table 1). In all there were 33 girls. The age range extended from 2.9 years to 14 years. Scifo *et al.* (1991) did not elaborate on the ages of individual children but stated that the age range was between 7 and 16 years with average age 11.6 years. Leboyer *et al.* (1992) had a 19-year-old participant whose data was not included in the review.

Comorbid conditions

One of the children in Kolmen *et al.*'s (1995) had a diagnosis of Down syndrome. There was one child with epilepsy amongst the participants in Scifo *et al.*'s (1991) study, one with possible diagnosis of Retts Syndrome and one with Pfieffer-Volklein syndrome. There were a child each with seizure disorder and situs inversus in both the studies by Willemsen-Swinkels *et al.* (1995, 1996). Williams *et al.* (2001) did not state whether the participants had any co morbid conditions.

Concurrent medication

The child with epilepsy in Scifo *et al.*'s (1991) study was on valproic acid, another child had promazine for difficulty in sleeping. The children with epilepsy in both the Willemsen-Swinkels studies (Willemsen-Swinkels *et al.* 1995, 1996) were on a fixed dose of carbamazepine during the trial period. Williams *et al.* (2001) did not state if any of the participating children were on any medication. None of the other children had been on any medication either before or during the trial.

Target symptoms

Bouvard *et al.* (1995) evaluated the plasma chemical changes in ASC children as an indirect measure of

Table 1 Population characteristics, target symptoms, outcomes side effects

Author/year	No.	Age	Sex M	Sex F	ID	ASD	Drug	Target symptoms	Outcome	Side effects	Jadad scores
Bouvard *et al.* 1995	10	5–14 years	5	5	Not stated 6 non-verbal	10	Naltx 0.5 mg/kg	Plasma chemical changes due to Naltx Rx and clinical symptoms of autism	As a group, there was marginal evidence for improvement with Naltx over placebo obscured by carryover effect of Naltx Subgroup of 4 children showed substantial clinical response	No side effects observed	R1B1 PI = 3
Campbell *et al.* 1990	18	3–8 years	14	4	PID to borderline ID	18	Naltx 0.5 mg raised to 1.0 mg/kg	Withdrawal Stereotypy hyperactivity aggression	Naltx group showed significantly greater improvement in CGCR ($P = 0.0068$) Improvement in hyperactivity in Rx group ($P = 0.069$) Greater effect on older than younger children ($P = 0.05$)	Weight loss 5/9 ↑Aggression (2) Stereotypy (2)	R1B2 PI = 4
Campbell *et al.* 1993	41	2.9–7.8 years	34	7	8 SID 9 Mod ID 14 MID 5 borderline 1 dull normal	41	Naltx 0.5 mg/kg for a week increased to 1.0 mg/kg or placebo	Behavioural symptoms Attentional learning	CGCR 7/18 improved on placebo, 13/23 on Naltx CPRS improvement in hyperactivity factor ($P = 0.0002$) Modest decrease in hyperactivity (CPRS), restlessness/over activity (PTQ) and carpet activity(significantly lower movement scores ($P = 0.045$) No effects on core symptoms of autism or discriminatory learning Naltx superior to placebo in ↓SIB	Weight loss 14/23 Drowsiness, Decreased appetite, Vomiting (1)	R1B2 PI = 4
Kolmen *et al.* 1995	13	3.4–8.3 years	12	1	DQ 21–115 9 with DQ < 70	13	Naltx 1 mg/kg	Hyperactivity Communication	Statistically significant improvement in CGI, IHF, SE- Restlessness (Parent) Significant improvement in teacher CGI considered improved in CGI only if better in 2 out of 3 settings – 8/13 showed modest improvement	Aggression (2) Drowsiness (1)	R1B2 PI = 4
Kolmen *et al.* 1997	11	4.7 years	9	2	Mean IQ 55	11	Naltx 1 mg/kg	Behaviour Learning	Statistically significant improvement on CGI but not compared with placebo No predictability for responsiveness	Drowsiness Decreased appetite Runny nose	R1B2 PI = 4
Leboyer *et al.* 1992	4	12–19 years Data on 19 year olds excluded	2	1	SID	4	Naltx 0.5, 1.0, 2.0 mg/kg	Behaviour and self-injury	Improvement in intensity and frequency of SIB in both low and high doses ↑Socialisation: improved eye to eye gaze and social exploration ↑Attention ↓Restlessness and temper tantrums	None recorded	R1B1 PI = 3
Scifo *et al.* 1991	12	7–16 years Average age 11.6 years	10	2	Only 2 were verbal and one with good cognitive level	12	Naltx 0.5, 1.0, 1.5 mg/kg	Autistic symptoms	Group analysis: BSE–Naltx ratings significantly lower than baseline ($P < 0.005$) at all levels and placebo ($P = 0.005$) CARS–Naltx ratings significantly lower only at 1 mg/kg ($P < 0.05$) Individuals – 7 were responders; 4 ↓in BSE only and 3 ↓ BSE and CARS	None observed	R0B1 PI = 2
Williams *et al.* 2001	8 2 excluded	2 years 10 months to 9 years 2 months	8	0	Not stated	8	Naltrex 1.5 mg/kg	Social behaviour changes	4/6 showed ↑ social interaction 5/6 improved GARS scores – stereotypies 4/6 improved attention None of these statistically significant	No side effects	R1B2 PI = 4
Willemsen-Swinkels *et al.* 1995	23 3 excluded	3–7 years	16	4	DQ > 40 (4) 40–55 (2) 55–70 (4) VQ 64–104 (the rest)	23	Naltx 40 mg single dose (1.48–2.35 mg/kg)	Temper tantrums hyperactivity Irritability social behaviours	Statistically significant effect on TARGET – temper tantrums and hyperactivity decreased Statistically significant reduction in irritability sub-scale of ABC Naltx failed to affect social behaviours	Sedation (8)	R1B2 PI = 4
Willemsen-Swinkels *et al.* 1996	23 3 excluded	3–7 years	16	4	<40–104	23	Naltx 0.74–1.18 mg/kg	Social behaviour Hyperactivity Irritability	No untoward side effects No significant differences in behaviour overall but some improvement in hyperactivity scores No improvement in social reciprocity	No untoward side effects	R1B2 PI = 4

R = Randomisation, B = Blinding, P = Account of all patients.
Naltr, naltrexone; BSE, behavioural summarised evaluation; CARS, Childhood Autism Rating Scale; CGCR, Clinical Global Consensus Ratings; CGI, clinical global impression; CPRS, Children's Psychiatric Rating Scale; DQ, developmental quotient; GARS, Gillian Autism Rating Scale; ID, intellectual disability; IHF, impulsivity hyperactivity factor; MID, mild intellectual disability; Mod ID, moderate intellectual disability; PID, profound intellectual disability; PTQ, Parent, Teacher Questionnaire; SE, side effect; SIB, self-injurious behaviour; SID, severe intellectual disability; TARGET, individualised checklist of five target symptoms per child; VQ, verbal quotient.

Table 2 Study design, duration, outcome measures and side effect measurements

Author/year	Drug	Design	Study period	Outcome measures	Side effect measurements
Bouvard *et al.* 1995	Naltx 0.5 mg/kg	Group 1 Placebo 4 weeks Naltx 4 weeks Group 2 Naltx 4 weeks Placebo 4 weeks	8 weeks	Childhood Psychiatric Rating Scale Behavioural Summarised Evaluation Abbreviated Connors Parent and Teacher Rating Scale Blood serotonin, plasma catecholamines and neuropeptides	No standardised measures used
Campbell *et al.* 1990	Naltx 0.5 mg raised to 1.0 mg/kg	Parallel group design –Baseline Placebo 2 weeks Naltx or placebo for 3 weeks Placebo 1 week	6 weeks	CPRS, CGI Clinical Global Consensus ratings (CGCR) Discrimination learning ECG, HR, RR, PR, BP, LFT	Naltrexone side effects checklist
Campbell *et al.* 1993	Naltx 0.5 mg/kg for a week increased to 1.0 mg/kg or placebo	Parallel group design-2 weeks placebo baseline Group A Naltx 3 weeks and 1 week placebo Group B Placebo 3 weeks and 1 week placebo	6 weeks	Child Psychiatric rating Scale CGI Nurse's Global Impression Aggression Rating Scale PTQ Clinical Global Consensus Rating- CGCR Weight BP, HR, RR, PR, LFT	Naltx side effects checklist
Kolmen *et al.* 1995	Naltx 1 mg/kg	Placebo 2 weeks Placebo/Naltx 2 weeks, washout 1 week Naltx/Placebo 2 weeks	7 weeks	CGI Connors Parent and Teacher Scales Parents Hyperactivity Impulsivity Factor (IHF) Restlessness	Naltrexone Side Effect Scale
Kolmen *et al.* 1997 Leboyer *et al.* 1992	Naltx 1 mg/kg Naltx 0.5, 1.0, 2.0 mg/kg	2 week drug/placebo with crossover with 2–7 days washout out between phases Each treatment and placebo given for a full week in arandomised order	7 weeks 4 weeks	CGI Connors Parents and Teachers Scale Home and school indices of change CGI Behaviour summarised evaluation (BSE) Levels of beta endorphin, Argenine vasopressin and unconjugated catecholamines	Naltx Side Effects Rating Scale
Scifo *et al.* 1991	Naltx 0.5, 1.0, 1.5 mg/kg	1 week baseline assessments, Naltrex administered every 48 h in the evening for 5 weeks at each dose, both Naltrex and Placebo subgroups treated for 15 weeks	30 weeks	Behavioural summarised evaluation (BSE) Childhood Autism Rating Scale (CARS) Beta Endorphin levels	Liver function tests
Williams *et al.* 2001	Naltrex 1.5 mg/kg	Phase 1 4 weeks, 1 week washout, Phase 2 4 weeks	9 weeks	Video observation CGI – Parents and clinicians CARS Behaviour checklists, Parenting Stress Index Distractibility Scale or Child behaviour checklist – Attention problem scale, GARS	Side effect interviews
Willemsen-Swinkels *et al.* 1995	Naltx 40 mg single dose (1.48–2.35 mg/kg)	Baseline Single dose Placebo and Naltx separated by 11 weeks AB or BA sequence	11 weeks	Aberrant behaviour checklist 12 items from Matson evaluation of social skills parents checklist of Target Symptoms – TARGET Monitoring of play room sessions. Liver function tests cortisol and beta endorphin levels	Liver function tests
Willemsen-Swinkels *et al.* 1996	Naltx 0.74–1.18 mg/kg	Naltx – placebo or placebo – Naltx Each Rx block with 2 weeks' baseline, 4 weeks' active Rx and 4 weeks' washout	20 weeks	Aberrant behaviour checklist Matson evaluation of social skills with Youngster TAR checklist for target symptoms	Weight measurements interview with parents and teachers

BP, blood pressure; CARS, Childhood Autism Rating Scale; CGI, Clinical global impression; CPRS, Children's Psychiatric Rating Scale; ECG, electrocardiogram; GARS, Gillian Autism Rating Scale; HR, heart rate; LFT, liver function test; PR, pulse rate; PTQ, Parents Teachers Questionnaire; RR, respiratory rate; Rx, treatment; TARGET/TAR, individualised checklist of five target symptoms/child.

low dose naltrexone and whether there were any predictive trends between clinical changes and plasma parameters. Campbell *et al.* (1990) assessed the therapeutic efficacy of naltrexone on PB as well as its effects on learning. PB included withdrawal, stereotypy, hyperactivity and aggression. Campbell *et al.* (1993) also focussed on safety and efficacy of naltrexone and its effect on behavioural symptoms of ASC, i.e. stereotypy, hyperactivity and aggression and attentional learning. Kolmen *et al.* (1995) evaluated the efficacy and safety of naltrexone on behaviours – hyperactivity and attention – and communication skills while Kolmen *et al.* (1997) focussed again hyperactivity and attention and also on learning. On the other hand Leboyer *et al.* (1992) studied the therapeutic efficacy of naltrexone on clinical features of ASC as well as SIB. Scifo *et al.* (1991), however, investigated the effects of naltrexone on behaviours related to ASC such as stereotypy, withdrawal and attention and plasma beta endorphin levels and Williams *et al.* (2001) studied social behaviours associated with ASC. Willemsen-Swinkels *et al.* (1995) studied the immediate effects of a single dose of naltrexone on social behaviours and in their 1997 paper the effects of longer term administration on the same behaviours.

Dosage

Table 2 summarises the dosage of naltrexone and the design used in the different studies. Only Campbell *et al.* used parallel design, all the other RCTs used a crossover design. In their 1990 study, Campbell *et al.* allocated children randomly to naltrexone or placebo treatment for 3 weeks followed by a 1 week placebo period. They used the same design in their 1993 study; the only difference was that the naltrexone dosage was increased after a week.

Bouvard *et al.* (1995) compared the effect of once daily dose of naltrexone 0.5 mg/kg with placebo, the sequence of treatment being randomly allocated so that half the children had 4 weeks of naltrexone followed by 4 weeks of placebo and the other half had the sequence in reverse. Kolmen *et al.* (1995) gave the participants either placebo or naltrexone as a single daily dose after 2 weeks of placebo, crossing over to naltrexone or placebo after a week's washout. Kolmen *et al.* (1997) used a similar design to Kolmen *et al.*'s (1995) previous study, with the difference that the children were given placebo during the washout period.

Leboyer *et al.* (1992) gave the participants a week each of daily doses of 0.5 mg, 1 mg and 2 mg/kg of naltrexone and placebo in a randomised order. Scifo *et al.* (1991) administered 0.5, 1 and 1.5 mg/kg of naltrexone every 48 h for 5 weeks each and placebo for 15 weeks. Williams *et al.* (2001) used 1.5 mg/kg of naltrexone every other day with drug or placebo phase for 4 weeks, the opposite phase for another 4 weeks with a week's wash out period. Willemsen-Swinkels *et al.* (1995) used single doses of naltrexone 40 mg (1.48–2.35 mg/kg) or placebo separated by 11 weeks. In their 1996 study, Willemsen-Swinkels *et al.* used naltrexone (0.74–1.18 mg/kg) everyday or placebo with each treatment block consisting of 2 weeks' baseline, 4 weeks' treatment and 4 weeks' washout.

Outcome measures

Outcome measures used are summarised in Table 2, some measures were used to assess the effect of naltrexone on behaviours associated with ASC. The Childhood Autism Scale (CARS) (Schopler *et al.* 1988) was used by Scifo *et al.* (1991) and Williams *et al.* (2001), the Gilliam Autism Rating Scale (GARS) (Gilliam 1995) was also used in the latter study. The Childhood Psychiatric Rating Scale (CPRS) (Fish 1985) was used by Bouvard *et al.* (1995) and Campbell *et al.* (1990, 1993). Behavioural Summarised Evaluation (BSE) (Barthelemy *et al.* 1990) was used by Bouvard *et al.* (1995), Leboyer *et al.* (1992) and Scifo *et al.* (1991). Clinical Global Improvement (CGI) (Guy 1976) was the commonest measure and was used in a number of studies including that of Campbell *et al.* (1990, 1993), Kolmen *et al.* (1995, 1997), Leboyer *et al.* (1992) and Williams *et al.* (2001). Campbell *et al.* (1990, 1993) also used Clinical Global Consensus Ratings (CGCR) (Campbell *et al.* 1984, 1997). Connors Parents and Teacher Rating Scales (Goyette *et al.* 1978) were used by Bouvard *et al.* (1995) and Kolmen *et al.* (1995, 1997) while Campbell *et al.* (1993) used Aggression Rating Scale, which was developed in their unit. Campbell *et al.* (1990, 1993) also used Parent–Teacher

Questionnaire (PTQ) (Guy 1976). Williams *et al.* (2001) used behaviour check lists, Parenting Stress Index – Distractibility Scale (Abidin 1995) and child behaviour checklist (Achenbach 1991) to study attention problems. Willemsen-Swinkels *et al.* (1995, 1996) used Aberrant behaviour checklist (Aman *et al.* 1985), Matson's Evaluation of Social Skills (Matson *et al.* 1985) and in addition completed a checklist with parents of 5 target symptoms specific for each child.

Campbell *et al.* (1990) also used Discrimination Learning (Anderson *et al.* 1984; Campbell *et al.* 1988) while Williams *et al.* (2001) used video recordings. Adverse effects were monitored using an unpublished naltrexone side effect checklist by Campbell *et al.* (1990, 1993), Naltrexone Side Effect Scale (Barron & Sandman 1993) by Kolmen *et al.* (1997) and Side Effects Interview by Williams *et al.* (2001). Campbell *et al.* (1990) monitored ECG, heart rate, respiratory and pulse rate, blood pressure and liver function tests and in their 1993 study, monitored weight.

Clinical outcomes

A total 155 children participated in 10 studies; 27 received placebo. Of the 128 that received naltrexone 98 (77%) showed statistically significant improvement in symptoms of irritability and hyperactivity.

Data from the 19-year-old child in Leboyer *et al.* (1992) was excluded on account of age. Bouvard *et al.* (1995) found a marginal evidence for improvement with naltrexone with the magnitude of the overall results being small and potentially obscured by carry over effects especially from naltrexone to placebo and naltrexone to post treatment periods. Campbell *et al.* (1990) found that the naltrexone group showed significantly greater improvement of CGCR ($P = 0.0068$) though other behaviour ratings did not confirm this result. In their 1993 study CGCR scores improved in 13 out of (56.5%) children who received naltrexone but also in 7 out of 18 (39%) who had placebo. Statistically significant improvement was found in both parents' and teachers' CGI ratings when naltrexone was compared to both baseline and placebo. In their replication study (1997), the improvement on parents' and teachers' CGI was statistically significant only when naltrexone was compared with baseline and not against placebo. When the results of the 1995 sample were combined with replication study sample, both parent and teacher CGI scores were significantly improved compared with baseline and placebo. Scifo *et al.* (1991) found on group analysis on BSE, ratings were significantly lower at all three doses of naltrexone compared with base line and placebo. Willemsen-Swinkels *et al.* (1995) administered a single 40 mg dose of naltrexone and placebo and found that naltrexone reduced irritability and target scores on behaviour checklists significantly. When they gave naltrexone over a 4 week period, parents could not distinguish between drug and placebo and both treatments appeared to improve behaviours compared with baseline ratings (1996). Campbell *et al.* in 1990 found that the treatment group showed improvement in the hyperactivity ($P = 0.069$) with older children responding more favourably to naltrexone than younger children ($P = 0.05$). In the 1993 trial, the improvement in hyperactivity factor on CPRS with naltrexone was significant at $P = 0.0002$ for the drug. There was also an improvement on restlessness/over activity on PTQ ($P = 0.035$) and a reduction in movement scores on carpet activity ($P = 0.045$). Kolmen *et al.* (1995) found statistically significant improvement in parents' ratings on impulsivity hyperactivity factor on Connors Parent Rating Scale and restlessness on Naltrexone Side Effects Rating Scale with naltrexone compared with baseline and placebo trials but improvement on Teacher Hyperactivity Factor of Connors rating scale was only significant compared with baseline and not against placebo. The parent measures on CPRS and Naltrexone Side effects Rating Scale showed significant improvement in Kolmen *et al.*'s replication study of 1997 against baseline but not placebo but when combined with the replication study sample, both parents scores and teachers' Restlessness scores on the Side effects check list showed significant difference both against baseline and placebo. Leboyer *et al.* (1992) found that restlessness was reduced in the two children who initiated play with increased attentiveness. At 1 m/kg/day, there was a deterioration which diminished at 2 mg/kg/day. Willemsen-Swinkels *et al.* (1996) found that teachers rated naltrexone treatment significantly better compared with placebo with reduction in hyperac-

tivity and irritability. Campbell *et al.* (1993) found that naltrexone had no effect on the core symptoms of autism or on discrimination learning and was not superior to placebo in reducing self-injury. Kolmen *et al.* (1997) also did not find naltrexone to be associated with improvement in learning. Leboyer *et al.* (1992) found that with naltrexone, resistance to change and temper tantrums were eliminated and self-injury improved at the lowest and highest doses of naltrexone. In Scifo *et al.* (1991), The CARS ratings were reduced at all three doses although it was statistically significant only at 1.0 mg/kg compared with baseline. They were also significantly lower on naltrexone compared with placebo. Williams *et al.* (2001) found that with naltrexone, 4 out of 6 subjects showed increase in social initiation, improved scores on the social scale of GARS and improvement of attention problems. Five out of 6 also showed improved scores on stereotypies scale of GARS. Statistical significance was not carried out due to the small number of subjects. Willemsen-Swinkels *et al.* (1995) did not find any improvement in social behaviour either in the single dose or 4 week administration of naltrexone.

Bouvard *et al.* (1995) found that a subgroup of four children who had elevated argenine vasopressin and 5 hydroxytryptamine serum levels showed substantial clinical response with treatment and their plasma chemistries returned to normal levels. In Leboyer *et al.* (1992), 2 of 3 participants had abnormal neurohumoral profiles and they showed clear behavioural improvements at the highest and lowest dose with diminution of withdrawal, an increase in social relatedness and proximity seeking behaviour. Scifo *et al.* (1991) did not find a correlation between clinical condition and plasma endorphin levels.

Adverse effects

No adverse effects were observed in the studies by Bouvard *et al.* (1995), Scifo *et al.* (1991), Williams *et al.* (2001) and Willemsen-Swinkels *et al.* (1996). None were recorded by Leboyer *et al.* (1992). Weight loss was observed in both papers by Campbell *et al.* (1990, 1993). Behaviour changes were noted in four of the children on naltrexone in the study by Campbell *et al.* (1990) and in two in the study by Kolmen *et al.* (1995). Drowsiness was noted in one child in the study by Kolmen *et al.* (1995); however, in the 1997 publication by the same group reported drowsiness in a greater number of children on naltrexone. Willemsen-Swinkels *et al.* (1995) reported sedation in eight out of the twenty children who received a single dose of naltrexone.

Jadad scores

On the Jadad scale for RCTs, the study by Scifo *et al.* (1991) scored the lowest at 2 as randomisation was not mentioned. On the other hand the studies by Bouvard *et al.* (1995) and Leboyer *et al.* (1992) each scored 3 while all the others scored 4 as they had all provided additional information on how blinding was achieved.

Discussion

There were 10 double blind placebo-controlled trials which studied the effect of naltrexone on PB in children with ASC and there was data available for 128 who had received active treatment and 27 on placebo. Williams *et al.* (2001) have not stated the level of functioning of the participants and all the participants in Leboyer *et al.* (1992) had severe ID. All the other studies include children both without ID and all levels of ID. Seven of the trials were conducted on outpatients and boys outnumbered girls (125 boys, 30 girls). The studies therefore cover children who would be representative of those seen in routine practice. Campbell *et al.* (1990, 1993) used a parallel group design. All the other studies are randomised control trial with a crossover design. They have the benefits of using a smaller sample size as the subject is their own control and as the within patient variance is smaller than between patient variance, there is correlation between patient's response to different treatments. This is an advantage where the number of eligible subjects is small.

On oral ingestion, naltrexone's onset of action is in 15–30 min with duration of action being 24–72 h with a peak effect in 6–12 h and is a potent opioid receptor blocker. The duration of active treatment was in excess of 2 weeks in all the studies except Willemsen-Swinkels *et al.* (1995) where the aim was to study the effects of acute administration of

naltrexone. As naltrexone acts quickly, the length of treatment in the trials was adequate. The carry over effect was taken into consideration and in terms of pharmacodynamics all the studies had adequate wash out periods between treatments. However, a crossover period of a few weeks may not be sufficient for the treatment of an enduring behaviour as opposed to biochemical change such as blood glucose level. Another problem is the short follow-up period as in clinical practice it is evident that behaviours associated with ASC are long standing and tend to fluctuate in the short run so that any improvement may be part of the natural course or trajectory.

Elbourne *et al.* (2002) have suggested a methodology for using continuous data from crossover studies for a meta analysis. In a systematic review, RCTs with crossover design can only be used qualitatively as simply pooling data from different periods may exaggerate the benefits of the more successful treatment. For this reason a meta analysis could not be done with the data.

None of the trials undertook a priori sample size calculations. Leboyer *et al.* (1992) only had three children in their sample and Williams *et al.* (2001) had six. The other studies had data for 10–41 children. All the studies used established outcome measures, Clinical Global Outcome being used most often.

The commonest adverse effect reported was weight loss; five out of nine children (55.6%) of children in Campbell *et al.* (1990) and 14 out of 23 (60.9%) children in Campbell *et al.* (1993) experienced this. One child had decreased appetite and vomiting. Ten children experienced drowsiness, 4 showed increase in aggression and 2 increase in stereotypy. This would suggest that naltrexone is well tolerated. The authors however comment on the difficulty in administering naltrexone as it has a bitter taste and this had to be duplicated in the placebo. Only 3 children were on concomitant medication during the trials; once each in Scifo *et al.* (1991) and the two studies by Willemsen-Swinkels *et al.* (1995, 1996) on anticonvulsant medication and one in Scifo *et al.* (1991) had promazine as a sedative. The results observed cannot therefore be attributed to concomitant medications used in the trials. Campbell *et al.* (1990, 1993), Kolmen *et al.* (1995, 1997) and Willemsen-Swinkels *et al.* (1995, 1996) found significant reduction in hyperactivity but no change in the core features of autism. Scifo *et al.* (1991) and Williams *et al.* (2001) found improvements on scales rating autism but the numbers of participants in both the trials are too small to draw a conclusion. Leboyer *et al.* (1992) found improvement on socialisation in 2 of their 3 participants. Bouvard *et al.* (1995) and Leboyer *et al.* (1992) found that in small number of children with elevated beta endorphin levels, normalisation with naltrexone was associated with improvement in behaviour but this was not corroborated by Scifo *et al.* (1991) who did not find a significant relationship between beta endorphin levels and behavioural ratings or difference in levels during naltrexone and placebo periods.

Data from 4 participants was excluded in Campbell *et al.* (1993), from 3 each in Kolmen *et al.* (1995, 1997), from 2 in Williams *et al.* (2001) and 3 each in Willemsen-Swinkels *et al.* (1995, 1996). None of them carried out Intent to Treat analysis.

In summary, naltrexone may improve hyperactivity and restlessness in children with autism but there was not sufficient evidence that it had an impact on core features of autism in majority of the participants. It is likely that a subgroup of children with autism and abnormal endorphin levels may respond to naltrexone and identifying the characteristics of these children must become a priority.

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