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The effectiveness of pharmacological
therapies for young people and adults with
Autism Spectrum Disorder (ASD)

A critical appraisal of the literature

Marita Broadstock and Carolyn Doughty

New Zealand
Health Technology Assessment

Department of Public Health and General Practice
Christchurch School of Medicine
Christchurch, NZ.

Division of Health Sciences, University of Otago

NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT (NZHTA)
THE CLEARING HOUSE FOR HEALTH OUTCOMES AND
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Department of Public Health and General Practice
Christchurch School of Medicine, Christchurch, New Zealand

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CONTACT DETAILS

New Zealand Health Technology Assessment (NZHTA)
The Clearing House for Health Outcomes and Health Technology Assessment
Department of Public Health and General Practice
Christchurch School of Medicine and Health Sciences
PO Box 4345
Christchurch
New Zealand
Tel: +64 3 364 1152 Fax: +64 3 364 1152

Email: nzhta@chmeds.ac.nz

Web Site: <http://nzhta.chmeds.ac.nz/>

EXECUTIVE SUMMARY

Objective

The purpose of this review was to systematically identify and appraise international evidence for the effectiveness and safety of drug therapy interventions used in managing Autism Spectrum Disorder (ASD) in young people and adults. The review was developed to inform an intersectoral New Zealand Best Practice Guideline for people with ASD and their carers/family/whanau being developed by the New Zealand Ministry of Health's Disability Services Directorate.

Data sources

The literature was searched using the following bibliographic databases: Amed, Cinahl, Embase, Index New Zealand, International Pharmaceutical Abstracts, Medline, PsychInfo, and Web of Science. Other electronic and library catalogue sources searched included: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), Evidence-based medicine reviews, Health Technology Assessment database, and the NHS Economic Evaluation database. Additional sources searched included major online library catalogues, major website sources such as evidence-based and guidelines sites, government health sites, and related health professional association websites. Relevant publications referenced in material obtained in the course of research on the topic were also identified.

Searches were limited to English language material from 1980 to February 2003 inclusive.

Selection criteria

Primary research studies were included if they met the following inclusion criteria:

- published in the English language, during or since 1980
- reported on samples of at least 10 people, primarily with ASD (at least 75% of the sample), with a mean/median age of at least 13 years
- evaluated pharmacological interventions currently available internationally which are aimed at treating or managing symptoms and associated conditions of ASD compared with the same drug at a different dose, placebo or usual care
- measured (using at least one standardised and/or quantitative outcome measure) effectiveness of the intervention in achieving improvement of core and/or associated features of ASD or quality of life for the person with ASD or their family/carers.

Studies were excluded if they primarily concerned participants with dementia, were case series reports, or were narrative (non-systematic) reviews, correspondence, book chapters, or articles published in abstract form.

Systematic reviews were considered which had study selection criteria that at least overlapped with those of the current review and therefore had the possibility of including papers eligible for this review, even if no such papers were identified.

Data extraction and synthesis

A systematic method of literature searching, selection and appraisal was employed in the preparation of this report. Abstracts (where available) identified from the search strategy, including references cited in retrieved articles, were scanned and excluded as appropriate. The full text articles were retrieved for the remaining studies and the authors (Ms Broadstock and Dr Doughty) independently applied

predetermined selection criteria to identify primary studies for appraisal. Concordance in selection was 100 percent. A single researcher (Ms Broadstock or Dr Doughty) performed each study appraisal and classified primary studies according to National Health and Medical Research Council (NHMRC 2000) levels of evidence criteria. Each study was critically described in Evidence Tables, and summarised and discussed in the text.

Key results and conclusions

The following conclusions are based on the current evidence available from this report's critical appraisal of literature published on the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder. Of more than 1,500 articles identified by the search strategy, 50 articles were retrieved as full text. From these, a final group of seven systematic reviews and five primary studies were identified as eligible for appraisal and inclusion in the review.

Seven systematic reviews were appraised that considered a range of pharmacological interventions, including atypical antipsychotics, anticonvulsants, secretin and vitamin therapy.

- Most of the reviews focused predominantly on children, although studies that included adolescents or adults were not excluded.
- The authors of one of the reviews concluded that there is some evidence that risperidone may be effective in reducing hyperactivity, aggression and repetitive behaviours in those with autism.
- All of the reviews highlighted the need for more double-blind, randomised controlled trials in this field and emphasised the ways in which recruitment, implementation and reporting of drug trials for ASD could be improved in the future.

The five primary research studies that met selection criteria for relevance and methodological quality were all double-blind, randomised placebo-controlled trials. All had relatively small sample sizes (mean = 30), were likely to be statistically underpowered, and had relatively brief treatment duration of no more than 12 weeks. Given study limitations, the primary research studies appraised provided only preliminary evidence relating to the (at least short-term) effectiveness of medications investigated.

- Risperidone (atypical antipsychotic) may be effective in reducing certain behaviours associated with autism, namely aggression, repetitive behaviour and hyperactivity, though not social functioning and language.
- Fluvoxamine (SSRI antidepressant) may be effective in reducing repetitive thoughts and behaviours, maladaptive behaviours and aggression. Fluvoxamine may also improve language usage, however it does not appear to influence sensorimotor behaviour, sensory response or social relationship to other people. Fluvoxamine is not currently available in New Zealand. It may be a useful addition to the range of medications that are available for people with ASD in this country.
- Haloperidol (typical antipsychotic) may be effective in reducing the overall severity of symptoms of autism as well as specifically reducing irritability and hyperactivity. Haloperidol may be more effective than clomipramine in the treatment of autism, although mean daily doses were lower for clomipramine than those routinely used in New Zealand. Neither drug appears to influence stereotypic behaviour, lethargy or inappropriate speech.
- Naltrexone hydrochloride (opiate antagonist) appears to be ineffective in the short-term. Neither a one-off moderate dose, nor four weeks of low or high-dose naltrexone, had a positive impact on behavioural features of autism or specifically on self-injurious behaviour.
- No major adverse events were reported for any of the interventions assessed in the primary studies. However, these small trials were not designed to determine risk estimates and reliable conclusions about these medications' safety profiles cannot be made.
- Generally speaking, no conclusions could be made about the effectiveness of one class of drug over another, or for the treatment of specific comorbidity.
- The range of drugs considered in the five studies appraised was not representative of the range of pharmacological interventions employed in clinical practice in New Zealand, suggesting that there

is a gap in knowledge on many commonly used medications in the management of people with autism.

- Medications are rarely the sole treatment modality for any individuals with autism. As an adjunctive treatment they may be effective with relatively few adverse effects and manageable side effects, although to date evidence is very limited. Larger sampled, double-blind, placebo-controlled trials are required that address the effectiveness and safety of drug interventions for both short and long-term treatment of adolescents and adults with ASD.
- While more research is required on agents that target associated symptoms that interfere with functioning or cause distress, development and evaluation of medications that show promise in treating core symptoms of social and language impairment in ASD should also be a priority.

MeSH headings

Index terms from Medline (MeSH terms): asperger syndrome, autistic disorder, rett syndrome, child development disorders pervasive, secretin, exp antipsychotic agents, exp psychotropic drugs, exp serotonin antagonists, exp dopamine antagonists, exp neurotransmitter uptake inhibitors, exp vitamin B, adult, adolescent.

Additional key words

Additional keywords (not standard index terms) were used in all databases: autis*, kanner's, child*, infant*, paediat*, pediat*.

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LIST OF ABBREVIATIONS AND ACRONYMS

5-HT	–	5-hydroxytryptamine (serotonin)
ABC-C	–	Aberrant Behaviour Checklist – Community
ANOVA	–	Analysis of Variance
ANCOVA	–	Analysis of Covariance
ASD	–	Autism Spectrum Disorder
CGI	–	Clinical Global Impressions Scale
c.f.	–	compared with
Cinahl	–	Cumulative Index to Nursing and Allied Health Literature
cVAS	–	clinical visual analogue scale
DAO	–	Duly Authorised Officer
DOTES	–	Dosage Treatment Emergent Symptom Scale
DSM-IV	–	Diagnostic and Statistical Manual of Mental Disorders 4 th Revised Edition
ECG	–	Electrocardiogram
ED	–	Emergency Department
EPS	–	extrapyramidal side effects
ESRS	–	Extrapyramidal Symptom Rating Scale
FDA	–	Food and Drug Administration
ICD-10	–	International Classification of Diseases 10 th Edition
IM	–	intramuscular (route of administration of drug)
IQ	–	intelligence quotient
LIPS	–	Leiter International Performance Scale
MAOI	–	monoamine oxidase inhibitor
mg/day	–	milligrams per day
mg/d/kg	–	milligrams per day per kilogram
MOH	–	Ministry of Health (NZ)
NHMRC	–	National Health and Medical Research Council
NHS	–	National Health Service (UK)
ns	–	not significant

NZHTA	–	New Zealand Health Technology Assessment (The Clearing House for Health Outcomes and Health Technology Assessment)
PDD	–	Pervasive Developmental Disorder
PDD NOS	–	Pervasive Developmental Disorder Not Otherwise Specified
PHARMAC	–	Pharmaceutical Management Agency of New Zealand
PO	–	oral (route of administration of drug)
PR interval	–	the interval on an ECG between the onset of atrial activity and the ventricular activity
PRN	–	as needed (from Latin translation)
QRS duration	–	ventricular electrical segment of the ECG cycle including the Q wave, R wave and S wave; it normally does not exceed 0.1 second
QT interval	–	the interval on an ECG that contains the deflections that are produced by ventricular contractions
RCT	–	randomised controlled trial
RF	–	Ritvo-Freeman Real Life Rating Scale
RR	–	relative risk
SIB-Q	–	Self-Injurious Behaviour Questionnaire
SR	–	systematic review
SSRI	–	serotonin re-uptake inhibitor
uHVA	–	urinary homovanillic acid
VAS	–	visual analogue scale
WAIS-R	–	Wechsler Adult Intelligence Scale-Revised
Y-BOCS	–	Yale-Brown Obsessive Compulsive Scale

GLOSSARY

Affect - the predominant emotion in a person's mental state.

Agranulocytosis - a disorder in which there is severe deficiency of certain blood cells (leucocytes) as a result of damage to the bone marrow by toxic drugs or chemicals. It is characterised by fever, with ulceration of the mouth and throat, and can lead rapidly to death.

Akathisia - a condition of motor restlessness in which there is a feeling of muscular quivering, an urge to move about constantly, and an inability to sit still often exhibited as pacing or rocking. Often accompanied by sensations of muscular discomfort, dysphoria and agitation.

Analysis of variance (ANOVA) - a statistical analysis involving the comparison of variance reflecting different sources of variability.

Agonist - a drug or other substance that acts at a cell-receptor site to produce an effect that is the same as, or similar to, that of the body's normal chemical messenger.

Antagonist - a drug or other substance with an opposite action to that of another drug or natural body chemical, which it inhibits.

Anxiolytic - anti-anxiety drug.

Before and after study - a situation in which the investigator compares outcomes before and after the introduction of a new intervention.

Bias - deviation of results or inferences from the truth, or processes leading to such deviation.

Blinded study - a study in which observers and/or subjects are kept ignorant of the group/intervention to which they are assigned.

Bonferroni correction - this is a multiple comparison technique used to adjust an error level (p value) to allow for multiple tests.

Bradykinesia - a symptom of parkinsonism comprising a difficulty in initiating movements and slowness in executing movements and maintaining body posture.

Case control study - an epidemiological study involving the observation of *cases* (persons with the condition) and a suitable *control* (comparison, reference) group of persons without the condition. The relationship of an attribute to the condition is examined by comparing *retrospectively* the past history of the people in the two groups with regard to how frequently the attribute is present.

Case series - a descriptive study of a subset of a defined population (i.e., a single patient or group of patients) which aims to describe the association between factors or attributes which the sample is exposed to, and the probability of occurrence of a given disease or other outcome. Case series are collections of individual case reports, which may occur within a fairly short period of time.

Coenzyme - a non-protein organic compound that in the presence of an enzyme, plays an essential role in the reaction that is catalysed by the enzyme.

Cohort study - the analytic method of epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed in different degrees, to a factor or factors hypothesised to influence the probability of occurrence of a given disease or other outcome. Studies usually involve the observation of a large population, for a prolonged period (years).

Confidence interval - the computed interval with a given probability – e.g., 95%, that the true value of a variable such as a mean, proportion, or rate is contained within the interval. The 95% CI is the range of values in which it is 95% certain that the true value lies for the whole population.

Confounder - a third variable that indirectly distorts the relationship between two other variables, because it is independently associated with each of the variables.

Confounding - a situation in which the measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s) that influence the outcome under study.

Dysarthria - impaired articulation of speech due to disturbances of muscular control.

Dyskinesia - group of involuntary movements that appear to be fragmentation of the normal smoothly controlled limb and facial movements.

Dyspepsia - disordered digestion: usually applied to pain or discomfort in the lower chest or abdomen after eating and sometimes accompanied by nausea or vomiting.

Dystonia - prolonged and unintentional muscular contractions of voluntary or involuntary muscles. It most often affects the large axial muscles of the trunk and limb girdles.

Effectiveness - a measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population.

Enuresis - the involuntary passing of urine.

Erythema - redness of the skin produced by congestion of the capillaries.

Ethology - the study of behaviour of animals in their normal environment.

Extrapyramidal side effects (EPS) - primarily neurological adverse events involving voluntary and involuntary musculature, including dystonias, parkinsonism, and akathisia.

Generalisability - applicability of the results to other populations.

Grey literature - that which is produced by all levels of government, academics, business and industry, in print and electronic formats, but which is not controlled by commercial publishers.

Hypertension - abnormally high blood pressure.

Hypotension - abnormally low blood pressure.

Intention-to-treat - a method for data analysis in a randomised controlled trial in which individual outcomes are analysed according to the group to which they were randomised, even if they never received the treatment to which they were assigned.

Meta-analysis - any systematic method that uses statistical analysis to integrate the data from a number of independent studies.

Mean - calculated by adding all the individual values in the group and dividing by the number of values in the group.

Median - any value that divides the probability distribution of a random variable in half. For a finite population or sample, the median is the middle value of an odd number of values (arranged in ascending order) or any value between the two middle values of an even number of values.

Neuroleptic malignant syndrome - major acute side effect of antipsychotics (neuroleptics) characterised by severe muscular rigidity, fever, an altered level of consciousness, and an autonomic instability.

Noradrenaline (or norepinephrine) - a hormone closely related to adrenaline and with similar actions, secreted by the medulla of the adrenal gland and also released as a neurotransmitter by sympathetic nerve endings.

Parenteral - administering a medication by injection through a route other than by alimentary canal (e.g., intramuscularly or intravenously).

Parkinsonism - a group of neurological disorders characterised by hypokinesia, tremor, and muscular rigidity. Antipsychotic induced parkinsonism is generally characterised by the triad of resting tremor, muscular rigidity, and bradykinesia (manifested as a mask-like facial expression or reduction of accessory limb movement, or as a problem of initiating movements). Other side effects include slowed cognition, worsening of negative symptoms, shuffling gait, and excessive salivation.

Polypharmacy - the administration of two or more drugs together.

Prevalence - the number of events in a given population at a designated time (point prevalence) or during a specified period (period prevalence).

Power - this is the probability that a statistical test or study will detect a defined pattern in data and declare the extent of the pattern as showing statistical significance.

Random sample - a sample that is arrived at by selecting sample units such that each possible unit has a fixed and determinate probability of selection.

Randomised controlled trial - an epidemiological experiment in which subjects in a population are randomly allocated into groups to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The groups are compared prospectively. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology.

Relative risk (RR) - the ratio of the risk of disease or death among the exposed to the risk among the unexposed. It is a measure of the strength or degree of association applicable to cohort studies and RCTs.

Selection bias - error due to systematic differences in characteristics between those who are selected for inclusion in a study and those who are not (or between those compared within a study and those who are not).

Serotonin (5-hydroxytryptamine/5-HT) - a compound widely distributed in the tissues, particularly the blood platelets, intestinal wall, and central nervous system. It acts as a neurotransmitter, and its levels are believed to have an important influence on mood.

Sialorrhea - the excessive production of saliva (also known as ptyalism).

Stereotypy - generally any condition characterised by a high degree of stereotyped behaviour and movement. Some authors restrict usage to psychopathological or neuropathological conditions; others will apply it to the normal recurrent mannerisms of those who are free of disorder.

Stereotyped movement - rigid, inflexible behaviour that tends to be made despite changes in the context and outcomes, which normally should produce modifications in how one acts.

Systematic review - literature review reporting a systematic method to search for, identify and appraise a number of independent studies.

Tardive dyskinesia - a group of involuntary movements that appear to be fragmentation of the normal smoothly controlled limb and facial movements after a longer period on medications. Usually considered irreversible.

Tachycardia - excessive rapidity in the action of the heart; the term is usually applied to a heart rate of above 100 beats per minute.

Tricyclic antidepressant - one of the most widely prescribed types of antidepressant, tricyclics are a group of drugs with a basic chemical structure of three benzene rings. Useful for treating a variety of different depressive symptoms, their side effects commonly include dry mouth, blurred vision, constipation, drowsiness and difficulty in urination.

Chapter 1: Background

1.1 OVERVIEW OF AUTISM SPECTRUM DISORDER

Autism is a life-long developmental disability which can affect communication, social interaction, and behaviour. Its form and severity can vary from person to person, but people with autism share some difficulty in making sense of the world. First illustrated in a series of case histories by Leo Kanner in 1943, it was not until 1980 that autism was officially recognised as a disorder of development distinct from childhood schizophrenia (Wing 1996a).

People with features similar to classic, Kanner-type autism have been identified who do not fulfil the same specific criteria for autism. To recognise this, a broader range of pervasive developmental disorders including Asperger's Syndrome, Pervasive Developmental Disorder – Not Otherwise Specified (PDD NOS)/Atypical Autism are now considered to be part of the autistic spectrum (although classification is contentious). This is collectively known as Autism Spectrum Disorder, or ASD. For simplicity, in this report we will use the term “autism” and ASD interchangeably to refer to people across the spectrum of ASD.

Core features

Core features of ASD are evident in three of the following behavioural areas (Aylott 2000; Folstein and Rosen-Sheidley 2001; Korkmaz 2000; Rapin 1997).

1. **Social interaction** - general difficulty with and lack of interest in developing social relationships. Not understanding fully the meaning of gestures, facial expressions, body postures, voice tone, and social cues to convey meaning and regulate social interactions. An absence of insight into what the other person is thinking (lacking in a “theory of mind”) or feeling (empathy).
2. **Language and communication** - language deficits lead to a delay or limitations in speech, including muteness in some people and difficulty in initiating or sustaining a conversation with others. Stereotyped and repetitive use of language which can be very literal, idiosyncratic and overly formal, marked by “over-learned scripts”. Speech is used to communicate needs and provide information rather than to exchange information or for social conversation. Difficulty in understanding figurative speech, including sarcasm, lies or irony. Lack of flexibility of thinking and imaginative activities.
3. **Restrictive interests and repetitive behaviour** - rigid and repetitive behaviour patterns including non-functional routines or rituals (e.g., touching doorknobs or walls). Inflexible adherence to behaviour and resistance to change in routine or to being interrupted. Stereotyped and repetitive motor mannerisms such as “hand flapping” when aroused or behaviours which are found to be pleasurable such as spinning car wheels or watching the same video repeatedly, and oral stereotyped movements such as humming or incessant questioning (Rapin 1997; Tager-Flusberg et al. 2001). A narrow, preoccupying interest in, for example, bus timetables, statistics or weather forecasts (Folstein and Rosen-Sheidley 2001), or parts of objects, which is abnormal in its intensity of focus.

Onset of abnormal or delayed functioning in at least one these areas is expected before the age of three years. These three areas are sometimes referred to as the “Triad of Impairment”. However, it is important to note that some researchers and people with ASD reject this “impairment model” of the condition and instead regard these features not as impairments but as differences to usual ways of being, which are not necessarily problematic or negative, or requiring treatment (Aylott 2000).

Associated features

Associated features of ASD sometimes evident include the following (Aylott 2000; Korkmaz 2000; Rapin 1997):

- unprovoked aggressive or violent behaviour to self and others, such as biting, head-banging and gouging
- attention and concentration problems
- sleep disturbance and a decreased need for sleep
- unusual responses to sensory stimuli
- special skills and interests, such as a talent for music, mathematics, visual-spatial abilities, or an exceptional memory for areas of knowledge of particular interest. Some individuals may have an outstanding rote visual or auditory memory and a high IQ.

At least 75 percent of people with autism exhibit some degree of intellectual disability (Rapin 1997; Stigler et al. 2002; Tager-Flusberg et al. 2001), although this figure has been questioned as being too high (Werry 2001) and it depends on how broadly the spectrum is being defined.

People with Asperger's Syndrome, which lies within the autistic spectrum of disorders, do not have speech delay, although their language can sound stilted or formal, and they can have social difficulties and a narrow range of interests (Rapin 1997). There is ongoing debate about the precise distinction between high functioning people with autism and people with Asperger's Syndrome (Tager-Flusberg et al. 2001).

Comorbidity

ASD can co-occur with any other physical, psychological or psychiatric condition. By adulthood, about a third of people with autistic disorders (depending on breadth of classification) will have had at least one epileptic seizure (Volkmar and Nelson 1990), with adolescence being the period when epileptic seizures are most likely to occur. Seizures are also common in those who also have intellectual disability. Tourette's Disorder can be comorbid with ASD and tics (as distinguished from stereotyped movements) are commonly seen in younger people with autism, although these may also appear as side effects of medication. People with ASD may be given diagnoses of obsessive-compulsive disorder, schizoid personality, schizophrenia, mood disorder, intellectual disability (known also as "mental retardation") and neurological conditions (Rapin 1997). Detachment and depression is common in adolescents and adults with ASD, especially those who are more able (Korkmaz 2000).

Classification of ASD

The triad of core features described earlier is the basis for diagnostic criteria used by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association 1994) and the International Classification of Diseases (ICD-10) (World Health Organization 1992) to classify ASD (see **Table 1, page 3**). Nevertheless, there is ongoing debate about the ability of these classifications to identify specific syndromes within the autistic spectrum (Wing 1996b), and other diagnostic codes may also be relevant.

Table 1. Diagnoses relevant to Autism Spectrum Disorders

Classification System	Disorders/syndromes (Code)
DSM-IV	<ul style="list-style-type: none"> ▪ Autistic Disorder (299.00) ▪ Pervasive Developmental Disorder – Not Otherwise Specified (299.80) ▪ Asperger's Syndrome (299.80) ▪ Rett's Disorder (299.00) ▪ Childhood disintegrative disorder (299.10)
ICD-10	<ul style="list-style-type: none"> ▪ Childhood autism (F84.0) ▪ Atypical autism (F84.1) ▪ Rett's Syndrome (F84.2) ▪ Asperger's Syndrome (F84.5) ▪ Other Pervasive Developmental Disorders (F84.8) ▪ Pervasive Developmental Disorder – unspecified (F84.9)

Aetiology and prevalence

Autism is currently only defined by behavioural criteria, although there is evidence for genetic influences (Folstein and Rosen-Sheidley 2001; Piven and Palmer 1999; Tager-Flusberg et al. 2001) and for ASD's association with conditions affecting the developing brain, such as tuberous sclerosis and maternal rubella (Wing 1996b). Neurobiological studies and biochemical studies are investigating evidence for abnormalities at the cellular and biochemical level.

ASD prevalence has been conservatively estimated as being between two and five per 10,000 (Bryson 1997). However, based on a review of epidemiological studies, Fombonne (2003) presented prevalence rates ranging from 0.7 to 21.1 per 10,000 when the full spectrum of disorders was included. Published prevalences are difficult to interpret as they tend to vary based on which definition of autism is used, and many studies report on relatively small populations, leading to a lack of precision in the prevalence estimate (Wing 1996b). Whilst some factors (e.g., migration) may have contributed to actual increases in reported prevalence, increases have been explained as largely due to a changing and broadening in diagnostic criteria employed across the spectrum, and increased early detection (Tager-Flusberg et al. 2001). At the individual level, autism affects three to four times more boys than girls (Smalley et al. 1988), although Rett's Disorder only affects girls.

1.2 FOCUS ON ADOLESCENTS AND ADULTS

Changes over the lifespan

Whilst most of the literature on management of autism through pharmacological interventions relates to children, there has recently been increased interest in the needs of adolescents and adults with autism. Reasons for this change in focus include that children within autism studies conducted in the 1970's and 1980's are now maturing, and that there are also many more people diagnosed as adolescents and adults than previously (Mesibov and Handlan 1997). Reporting on follow-up studies, Korkmaz (2000) discusses how diagnostic features, differential diagnosis, and the clinical problems of adults with autism differ substantially from those of children with autism. Autism tends to be apparent from the age of two to five years with a gradual overall improvement in symptoms between the ages of six and 10 years, fluctuating in adolescence and early adulthood. There are increasing adaptive skills in most people in middle adulthood and later life (Korkmaz 2000). Appropriate recognition of ASD and educational, behavioural and environmental management facilitate these improvements.

Changes over the lifecourse vary across the major clinical features of ASD, as discussed in a review by Korkmaz (2000). With respect to language ability, a longitudinal study of autistic disorder (Ballaban-Gil et al. 1996) found that 35 percent of people with autism had achieved at least near-normal fluency by adulthood and 29 percent of people had achieved at least near-normal comprehension of oral language. Social interests and skills greatly increase in adolescence and continue to develop in adulthood, although adults with autism still experience difficulty in establishing and maintaining

interpersonal relationships (Mesibov and Handlan 1997). Differences in social interaction most characteristic of adolescents and adults discussed by Rutter (1983) include a lack of reciprocity in social exchanges, limited physical contact, and a lack of understanding of others' thoughts and feelings.

Aggression and self-destructive behaviour can increase during adolescence (Mesibov and Handlan 1997). Ballaban-Gil's (1996) longitudinal study found that self-injurious behaviour was evident in 35 percent of adolescents and 49 percent of adults, and about half of the adolescents and adults with ASD reported stereotyped movements. Rituals, resistance to change, and preoccupations with specific topics of intense interest are common for high-functioning adults with ASD. The onset of puberty can raise challenges in terms of exposure, public masturbation and genital contact, although these behaviours are generally infrequent and can be managed with behavioural techniques and strategies which allow sexual needs to be met in socially acceptable ways (Mesibov and Handlan 1997).

There can be a flattening of affect with age (Rumsey et al. 1985). As mentioned earlier, depression is more likely to arise in adolescence or adulthood, possibly due to awareness of problems in social interaction associated to autism (Korkmaz 2000).

Transition to adulthood

Attainment of independence in adulthood is related strongly to level of ability (Wing 1996b). People with reasonable language skills, including those with Asperger's syndrome, tend to be more likely to be able to live independently than less communicative people with autism. The advent of group homes in the community has reduced the number of people with autism who require long-term institutional care (Korkmaz 2000), although institutionalisation is still apparent for a minority of people with autism (Mesibov and Handlan 1997). Nevertheless, less than five percent of people with autism are able to live fully independent lives as adults, one third have some degree of personal independence, and the majority remaining require high levels of support as adults in terms of residential care, occupation, and leisure activities (Howlin and Goode 1998)¹. However, the overall proportion of people with ASD who can live independently may have been underestimated, as those who are mildly affected may not ever be diagnosed (Rapin 1997).

Employment options can be limited with, according to one study, only 11 percent of adults with autism employed on the open market, and these in relatively unskilled jobs. A further 16 percent worked in sheltered workshops (Ballaban-Gil et al. 1996). Some "high functioning" people with autism become graduates of universities and achieve employment in select fields.

Unfortunately, psychiatric morbidity and behavioural problems, such as aggression, can increase in adolescence and adulthood (Korkmaz 2000; Larsen and Mouridsen 1997). Therefore, the transition between these phases of life, with the advent of the possibility of independent living, is a time when effective intervention may be particularly valuable for persons with ASD and their carers.

1.3 PHARMACOLOGICAL INTERVENTIONS

Findings from preliminary studies of major neurotransmitters and other neurochemical agents strongly suggest that neurochemical factors play a major role in the aetiology of autism. However, compared to the breadth of research into the aetiology and neurobiology of autism, there have been relatively few controlled studies that address the pharmacological treatment of ASD. Whilst there are no aetiologically based drug treatments available that specifically seek to cure autism (Santosh and Baird 2001), there is an extensive body of literature describing pharmacotherapy management of the symptoms and associated conditions of autism in children and adolescents, and to a lesser extent adults (Posey and McDougle 2001).

Although educational and behavioural treatments continue to form the mainstay of treatment for children and adolescents, increasingly interest is being shown in the role of medication as an adjunctive therapy in all age groups.

¹ As elsewhere, these estimates will vary depending on the classification of ASD.

This is reflected in the rates of psychotropic drug use. In a study in the United States, Martin et al. (1999) reported that 55 percent of 109 children, adolescents and adults (mean age=13.9 years, SD=6.9) with high functioning pervasive developmental disorders (PDDs) were taking psychotropics, with a further 40 percent taking antiepileptic medication concurrently. Antidepressants were the most commonly used agents (32%) followed by stimulants (20%) and antipsychotics (16%).

A variety of drugs are used to treat or manage symptoms and associated conditions of autism, including core and associated features, which are regarded as being problematic to those with autism and their carers, and which may affect quality of life and/or the ability to live independently. Several controlled studies have investigated the efficacy of a range of medications in the treatment of the associated symptoms of autism (Posey and McDougle 2000), including aggression, agitation, hyperactivity, inattention, irritability, repetitive behaviours and self-injury. Treatment of these disabling symptoms may allow other more non-pharmacological interventions (e.g., educational and behavioural) to proceed more smoothly and effectively. Medication may also be useful in assisting individuals with autism to live outside institutional settings (Posey and McDougle 2001).

A major factor in guiding clinicians' approach to choice of pharmacological treatment is an awareness of specific conditions comorbid with autism in an individual patient (Kerbeshian et al. 2001; Larkin 1997), including epilepsy, and obsessive compulsive, mood or anxiety disorders.

A number of non-systematic narrative reviews have been published that provide an overview of the pharmacotherapeutic management of autism in more detail (Kerbeshian et al. 2001; Posey and McDougle 2000; Posey and McDougle 2001; Tyrer and Hill 2000). A brief summary of the pharmacological medications used and researched for the management of autism is presented within this section.

Typical antipsychotics

Several studies have been conducted on various typical antipsychotics including haloperidol (Campbell et al. 1978) and pimozide (Naruse et al. 1982). While both are considered to be efficacious, concerns about the development of dyskinesias, including tardive dyskinesia (TD), have meant that use of typical antipsychotics, particularly haloperidol, has usually been reserved for individuals with severe symptoms (Posey and McDougle 2001). One of the benefits of haloperidol is that weight change is less commonly a side effect of treatment.

Atypical antipsychotics

Atypical antipsychotics are recognised for their ability to produce an antipsychotic effect in a majority of patients without inducing significant extrapyramidal side effects (McDougle et al. 2000). Extrapyramidal side effects include both early-onset and chronic neurological adverse events involving voluntary and involuntary musculature, the most common of which include parkinsonism (bradykinesia, rigidity, tremor), dystonias, and akathisia (Hughes 1999). Neuroleptic malignant syndrome is another major acute side effect that may be associated with the use of antipsychotics (neuroleptics). It is typically characterised by severe muscular rigidity, fever, an altered level of consciousness, and autonomic instability. Atypical antipsychotics (potent antagonists of serotonin and dopamine) have increased in popularity, given the lower incidence of tardive dyskinesia (in the short-term) (McDougle et al. 2000), and clinicians have begun to use these medications more in treating individuals with autism (McDougle et al. 1995a; McDougle et al. 1997; McDougle et al. 1998). Some atypical antipsychotics used with people with ASD are introduced below.

Risperidone

Risperidone is thought to be effective in improving hyperactivity and in reducing the frequency and intensity of temper outbursts and aggression, which are sometimes apparent as associated symptoms of people with autism, although there have been concerns about side effects such as sedation and weight gain (McDougle et al. 1998). At higher doses, extrapyramidal side effects may occur more frequently.

Olanzapine

Olanzapine has been used for treatment of aggression, hyperactivity, mood symptoms, sleep disturbance and psychosis occurring in autism (Potenza et al. 1999). Weight gain may also be a problematic side effect with this medication (Wirshing et al. 1999).

Clozapine

The use of clozapine has been described in a small case study of only three children (Zuddas et al. 1996). The limited use to date of clozapine may relate to the need for frequent tests to monitor white blood cell counts due to the risk of agranulocytosis, and also to an increased risk of seizures at high doses (Volkmar and Nelson 1990). This is particularly of note because individuals with autism are already at higher than normal risk of developing seizure disorders (Posey and McDougle 2001).

Antidepressants

A wide variety of antidepressant medications have been used in the treatment of autism for decades. This drug class comprises a broad grouping of chemical compounds that generally work by increasing the concentration (in the synaptic space) primarily of noradrenaline and/or serotonin (5-HT) (Kereshian et al. 2001).

Researchers have investigated whether the selective serotonin re-uptake inhibitors (SSRIs) may be of benefit in reducing repetitive behaviours, aggression and aspects of social relatedness in children, adolescents, and adults with autism. These medications have been considered safer alternatives than the tricyclic antidepressants, given their better tolerability and lack of significant cardiac effects (Posey and McDougle 2001).

Some examples of antidepressants used in managing ASD are outlined below.

Clomipramine

Clomipramine is a tricyclic antidepressant recognised for its potent inhibition of 5-HT uptake (i.e., acting as a nonselective serotonin re-uptake inhibitor). It has been shown to be more efficacious than the relatively selective noradrenaline-reuptake-inhibiting tricyclic desipramine in the treatment of children with obsessive-compulsive disorder (Leonard et al. 1989). The repetitive behaviours and stereotyped movements commonly seen in pervasive developmental disorders, including ASD resemble, in part, the compulsions seen in that disorder (McDougle et al. 1995b; Posey and McDougle 2000). The efficacy of clomipramine has been researched in studies of children, adolescents and adults with autism. There is some suggestion that clomipramine may be better tolerated by adolescents and adults compared with children (Sanchez et al. 1996).

Fluvoxamine

As potent inhibitors of 5-HT uptake, SSRIs such as fluvoxamine have received increasing attention as a treatment for the symptoms of autism because of their better side effect profiles compared to tricyclics such as clomipramine. Fluvoxamine appears to target a range of symptoms including repetitive thoughts and behaviour, maladaptive behaviour, aggression, and communicative use of language. However, lower efficacy and tolerability of fluvoxamine has been noted in children and adolescents with autism (Stigler et al. 2002). Fluvoxamine is not available in New Zealand.

Other examples of antidepressant medication (e.g., imipramine, trazodone, bupropion, venlafaxine, nefazadone, monoamine-oxidase inhibitors (MAOIs) and mirtazapine) may be used for managing symptoms of ASD. Trazodone and mirtazapine are not available for use in New Zealand, while bupropion and venlafaxine are available but not subsidised.

Fenfluramine

Fenfluramine is an indirect 5-HT receptor agonist with structural similarities to amphetamine. Several initial reports indicated that this agent may have been promising as a potential treatment for autism. An initial double-blind crossover study of fenfluramine and placebo was favourable (Ritvo et al. 1986). However, subsequent double-blind placebo-controlled trials failed to show consistent benefits with fenfluramine use in children (Campbell et al. 1988; Ekman et al. 1989; Sherman et al. 1989). Approved by the Food and Drug Administration (FDA) for the treatment of obesity, the drug was voluntarily withdrawn from the world market in 1997 because of concern that it contributed to the development of cardiac valvular disease (Connolly et al. 1997; Posey and McDougle 2000). For this reason, studies of this medication have been excluded from the current review.

Stimulants

Early studies of the effects of stimulants in children with autism generally produced negative results. Concerns were also expressed regarding the possibility that stimulants may lower the seizure threshold. This led to the widespread clinical view that stimulants were contraindicated in treating autism (Posey and McDougle 2000). However, some preliminary studies with children have suggested positive benefits with stimulant treatment relating to motor hyperactivity and inattention in autism (Birmaher et al. 1988; Quintana et al. 1995).

Anticonvulsants

It remains unclear whether anticonvulsants, such as lamotrigine, may be helpful in improving other clinical symptoms of autism in adolescents and adults, in addition to their effects in controlling seizure disorders (Belsito et al. 2001; Tsai 1999; Uvebrant and Bauziene 1994) although some preliminary work with sodium valproate has been promising (Hollander et al. 2001).

Lithium

Lithium is an alkaline metal salt that has actions on multiple neurotransmitter systems. It has been suggested that this agent may be effective for some individuals with ASD where there are symptoms resembling mania and positive family histories of bipolar disorder (Kerbeshian et al. 1987; Posey and McDougle 2000; Steingard and Biederman 1987).

Anxiolytics

Buspirone is a 5-HT_{1A} receptor partial agonist used in the treatment of generalised anxiety disorder that may also improve target symptoms of anxiety and irritability in those with PDD including autism (Buitelaar et al. 1998; King and Davanzo 1996).

α₂-Adrenergic-agonists

Clonidine

Clonidine has been reported as improving irritability, hyperactivity, stereotyped movements, inappropriate speech and oppositional behaviour of hyperactive and impulsive children (Jaselskis et al. 1992). Transdermal clonidine has been used in the treatment of people with ASD (Fankhauser et al. 1992).

Guanfacine

Guanfacine has been used to improve hyperactivity, inattention, insomnia and tics in individuals with autism (Stigler et al. 2002). Guanfacine is not available for use in New Zealand.

β-Adrenergic-antagonists

Propranolol has been used in treating aggression and self-injury in adults with autism and has also been reported as having a positive effect on socialisation and speech (Ratey et al. 1987).

Opiate antagonists

Excess opiate activity has been mooted as a contributing factor to the aberrant social and language development observed in individuals with autism, and the opiate antagonist naltrexone hydrochloride has been investigated for its efficacy in treating the core symptoms of autism (Willemsen-Swinkels et al. 1995) and reducing self-injurious behaviour (Stigler et al. 2002).

Miscellaneous

Secretin

Secretin, a gastrointestinal polypeptide hormone, is an agent recently to have received attention as a possible pharmacological treatment for ASD. Porcine secretin as well as synthesised human secretin administered intravenously has been used. Originally FDA-approved for use in the diagnosis of certain gastrointestinal diseases, secretin's use for the treatment of autism was popularised by a small study that reported its positive impact on language and social relatedness in three young children with autism (Horvath et al. 1998). However, subsequent controlled studies have been less favourable (Patel et al. 2002).

Immunotherapy

Vancomycin and intravenous immunoglobulin are also being investigated to see if their use results in any behavioural improvements in children with autism (DeGiudice-Asch et al. 1999; Sandler et al. 2000).

Vitamins, including pyridoxine

There have been claims that “mega” doses of certain vitamins and other agents may ameliorate or prevent a range of conditions, including ASD (Kerbesian et al. 2001). Agents investigated include vitamin B6, B12, folic acid, magnesium and melatonin. In general, vitamins act as coenzymes or enhancers of biochemical processes, many of which are involved in the synthesis and regulation of neurotransmitters and other polypeptide products. High doses of vitamins, especially pyridoxine, (vitamin B6) in conjunction with magnesium have been proposed as being helpful in autism by reducing aggressiveness, self-stimulation, and avoidance of eye contact, and improving social relatedness and speech (Martineau et al. 1985). Megadoses of vitamins are variable in their toxicity, depending on the vitamin used, and the effectiveness of vitamin therapies has been questioned (Findling et al. 1997).

Whilst it is evident that a great variety of pharmacological interventions have been employed in managing symptoms and associated conditions of autism, a much narrower range of interventions have been systematically evaluated in the research literature.

1.4 AVAILABILITY OF MEDICATIONS FOR ASD IN NEW ZEALAND

A variety of medications are available for use in the treatment of people with ASD in New Zealand; however, some specific pharmacological agents within individual classes are available but not subsidised for use in this country. Treatment algorithms employed by clinicians within New Zealand are influenced by both the availability of the agent and the potential cost to the patients and their carers, however the initial decision about medication are influenced to a large degree by the specific target symptom or suspected underlying comorbid psychiatric condition.

Several antipsychotic drugs are available for use including the atypical antipsychotic risperidone, but olanzapine use is uncommon in ASD as it is not yet subsidised for this. A range of tricyclic and SSRI antidepressants are also used. An indicative (though not comprehensive) list of medications commonly used in New Zealand for treating people with ASD is provided in **Table 2** below, with information provided about their subsidisation and requirements for approval. Notably, fluvoxamine is not available in New Zealand while bupropion, naltrexone, sertraline and venlafaxine are available but not subsidised.

Table 2. Pharmacological treatments used for treating ASD in New Zealand: subsidisation and requirements for confirmation.

Class/Name	Subsidised
Antipsychotics	
Haloperidol	Yes
Pimozide	Yes
Risperidone	Yes
Olanzapine	Yes ²
Quetiapine	Yes ¹
Clozapine	Yes ³
Tricyclics	
Clomipramine	Yes
Imipramine	Yes
Nortriptyline	Yes
Doxepin	Yes
SSRIs and related antidepressants	
Fluoxetine	Yes
Citalopram	Yes ¹
Paroxetine	Yes ¹
Sertraline	No
Venlafaxine	No
Nefazadone	Yes ¹
MAOIs including reversible agents	
Tranylcypromine	Yes
Moclobemide	Yes ¹
Other	
Bupropion	No
Naltrexone	No
Buspirone	Yes ²

¹ For a certified condition, special conditions apply

² Special authority required (approval from PHARMAC)

³ Specialist's recommendation

1.5 OBJECTIVE

Because of the immense impact autism has on the lives of affected individuals and their families/carers, hopes for cure have led to rapid uptake of new therapies without an established research base to investigate their efficacy (e.g., porcine secretin).

The purpose of this review was to systematically identify and appraise international evidence for the effectiveness and safety of drug therapy interventions used in managing ASD in young people and adults. The review was undertaken to inform an intersectoral New Zealand Best Practice Guideline for people with ASD and their carers/family/whanau which is being developed by the New Zealand Ministry of Health's Disability Services Directorate.

1.6 REVIEW SCOPE

Studies were included for review if they reported on the effectiveness of pharmacological therapy interventions used in managing ASD in young people and adults.

The search was limited to full reports published in English between 1980 and February 2003. Full details of inclusion and exclusion criteria are provided in the next chapter.

1.7 STRUCTURE OF REPORT

This report is divided into four chapters. Following this Background section, **Chapter 2** presents the Methodology section, which includes search strategy, inclusion and exclusion criteria, and outcomes considered. The results section (**Chapter 3**) of the review describes and synthesises primary and secondary research appraised. This chapter also provides detailed Evidence Tables which present each appraised study's methods, results, limitations and conclusions. Finally, the Discussion (**Chapter 4**) summarises results, outlines key methodological limitations and future directions in the area, and presents the review's conclusions.

Chapter 2: Methodology

2.1 SELECTION CRITERIA

Published studies were considered for this review if they used one of the following study designs:

- systematic review (SR) of studies eligible for inclusion in this review (see further criteria below)
- randomised controlled trials (including cross-over trials)
- pseudorandomised controlled trials (alternate allocation or some other method)
- concurrent controls or cohort studies
- case-control studies
- interrupted time series
- historical control, two or more single arm studies, or interrupted time series without a parallel control group.

Evidence obtained from case series, either post-test or pretest/post-test (“before and after”), were excluded (e.g., “open” trials without a control group). Any identified unpublished or “grey” literature was included for New Zealand specific studies only where it met selection criteria.

Inclusion and exclusion criteria for primary research studies are described in **Table 3** below.

Table 3. Inclusion/exclusion criteria for identification of relevant studies

Characteristic	Criteria
Inclusion criteria	
Publication type	Studies published 1980 or later.
Patient characteristics	Study population primarily those (at least 75% of sample) with Autism Spectrum Disorder (ASD) as classified by or consistent with DSM-IV and/or ICD-10 ² (see Table 1), or where results are reported separately for this group. Adolescents (aged 13 to 17 years) or adults (aged 18 years or more). Studies that were not restricted to participants within these age ranges, but where results were reported separately on a subgroup of participants aged at least 13 years.
Sample size	Studies with sample sizes of 10 or more people.
Intervention/test	Drugs aimed at treating or managing symptoms and associated conditions of ASD.
Comparator	Comparison drug, the same drug at a different dose, placebo, or usual care.
Outcome	Studies using at least one standardised and/or quantitative outcome measure relating to effectiveness of relevant interventions in achieving improvement of core features of ASD; improvement of associated features of ASD; global impression rating scales; and quality of life questionnaires for individuals with ASD and/or family/carers (see Section 2.5 for details). Where a study is included which reports on effectiveness, data reported on the safety profile of the drug were also considered, including side effects.
Exclusion criteria	
Publication type	Non-systematic reviews, letters, editorials, expert opinion articles, comments, book chapters, articles published in abstract form and studies on animal subjects, excluded. Non-published work excluded.

² As there is not complete agreement between classification systems (which have altered over time) or diagnostic methods for autism, the definitions used for ASD will be reported in the Evidence Tables for ease of comparison.

Table 3. Inclusion/exclusion criteria for identification of relevant studies (continued)

Characteristic	Criteria
Language	Non-English language articles excluded.
Study design	Evidence obtained from case series, either post-test or pre-test/post-test, excluded (Level IV evidence on NHMRC hierarchy).
Sample	Studies that reported outcomes for a study population including 50 percent or more outside the age range of 13 to 75 years, or with a mean or median sample age less than 13 years, excluded. Studies that primarily concerned participants with dementia, or people who were likely to be suffering from dementia (including studies of samples aged over 75), excluded.
Intervention/test	Studies investigating drugs that are no longer officially "on the market" internationally including fenfluramine (See Chapter 1)
Outcome	Studies reporting solely on safety without accompanying effectiveness data, excluded. Biochemical measures (for example, used as hypothetical markers of ASD or its aetiology) will not be reported as valid outcome measures.

Systematic reviews were considered which had study selection criteria that at least overlapped with those of the current review and therefore had the possibility of including papers eligible for this review, even if no such papers were identified. Systematic reviews were reviews which included the following features: a focused research question, explicit inclusion/exclusion criteria, explicit search strategy (including identified bibliographic databases), summary of included studies' results, and summary of review results.

2.2 SEARCH STRATEGY

A systematic method of literature searching and selection was employed in the preparation of this review. Searches were limited to English language material published from 1980 onwards. The searches were completed on 20 February 2003.

Principal sources of information

The following databases were searched (using the search strategy outlined in **Appendix 1**):

Bibliographic databases

Amed
Cinahl
Embase
Index New Zealand
International Pharmaceutical Abstracts
Medline
PsychInfo
Web of Science

Review databases

Cochrane Database of Systematic Reviews
Database of Abstracts of Reviews of Effectiveness
Evidence-based medicine reviews
Health Technology Assessment Database
NHS Economic Evaluation Database

Other sources

In the preliminary search undertaken for this review, additional sources searched included major online library catalogues, and major website sources such as evidence-based and guidelines sites, government health websites, and related health professional association websites.

Bibliographies of publications obtained in the course of research on the topic were also scanned by the authors to identify potentially eligible papers.

For more detail about the search sources refer to the NZHTA Search Protocol at <http://nzhta.chmeds.ac.nz/nzhtainfo/protocol.htm> Steps 1-15 (Core and Standard sections), and steps 16-17, 19-20 (Ideal section).

Handsearching of journals, contacting of manufacturers, or contacting of authors for unpublished research was not undertaken.

Main search terms used

- Index terms from Medline (MeSH terms): asperger syndrome, autistic disorder, rett syndrome, child development disorders – pervasive, secretin, exp antipsychotic agents, exp psychotropic drugs, exp serotonin antagonists, exp dopamine antagonists, exp neurotransmitter uptake inhibitors, exp vitamin B, adult, adolescent.
- Index terms from Embase: autism, asperger syndrome, rett syndrome, drug effect, drug efficacy, exp neuroleptic agent, exp psychotropic agent, exp serotonin antagonist, exp dopamine receptor blocking agent, pyridoxine, secretin, exp "agents interacting with transmitter, hormone or drug receptors", exp child, adult, exp adolescent.
- The above index terms were used as keywords in databases where index terms were not available and in those databases without controlled vocabulary.
- Additional keywords (not standard index terms) were used in all databases: autis*, kanner's, child*, infant*, paediat*, pediat*.
- Additional search techniques: registry number searches for 106266-06-2 (Risperidone) and 1393-25-5 (Secretin), floating sub-heading searches: drug therapy, drug dose, drug combination, and therapeutic use, and searches for letter as a publication type.

2.3 STUDY SELECTION

Studies were selected for appraisal using a two-stage process. Initially, the titles and abstracts (where available) identified from the search strategy, including references cited in retrieved papers and review articles, were scanned and excluded as appropriate. The full text articles were retrieved for the remaining studies. The authors (Ms Broadstock and Dr Doughty) independently identified primary research articles eligible for appraisal after applying predetermined selection criteria outlined above. Concordance in selection was 100 percent. A single researcher (Ms Broadstock or Dr Doughty) performed each study appraisal. The same researcher performed appraisal of primary research articles and relevant systematic reviews for each identified pharmacological drug group.

2.4 APPRAISAL OF STUDIES

The evaluation initially classified studies according to National Health and Medical Research Council (NHMRC 2000) levels of evidence criteria, so as to rank them in terms of quality according to a pre-determined "evidence hierarchy" (see **Appendix 2**). The levels describe groups of research, which are broadly associated with particular methodological limitations. However, these levels are only a general guide to quality because each study may be designed and/or conducted with particular strengths and weaknesses. High-level evidence is provided by a well-conducted randomised-controlled trial comparing a drug of interest and control/placebo/usual care.

Summaries of appraisal of primary studies are presented in **Evidence Tables** and include:

- authors, publication date, and country where study was principally conducted
- design
- evidence level (applying NHMRC criteria)
- description of intervention drug and comparator
- study design
- study setting
- patient characteristics including number of patients for intervention and comparator groups
- patient inclusion and exclusion criteria
- analyses comparing intervention and comparator groups at baseline
- detail of dosage, administration route, and timing of follow-up intervals relative to drug administration
- eligible outcome measures used for effectiveness and safety
- results of analyses comparing intervention and comparator groups on eligible outcomes, including statistically tested comparisons and reporting of relevant statistical data
- adverse events/side effects (and incidence) for the intervention and comparator groups
- authors' conclusions
- comments on the study's strengths and limitations relevant to its internal validity.

Systematic reviews are described in **Evidence Tables** and critiqued in terms of the following features (Buckingham et al. 2003):

- focused research question (relating to patients, exposures, outcomes)
- explicit inclusion/exclusion criteria (relating to patients, exposures, outcomes, methodological standards)
- explicit and comprehensive search strategy (e.g., bibliographic databases, reference lists, personal contacts)
- validity of included studies appraised
- similarity of results from study to study discussed
- reproducibility of assessment of studies (blinded reviewers, inter-observer agreement)
- summary of systematic review results provided.

Note: that such papers were considered principally as background information, as they invariably do not use the same selection criteria or publication period as the current review.

2.5 KEY OUTCOME MEASURES FOR PRIMARY STUDIES

Key outcomes considered were those using standardised and/or quantitative measures of the effectiveness of relevant interventions in achieving the following outcomes.

1. Improvement of core features of ASD, including:
 - social interaction (e.g., social relationship subscale of the Ritvo-Freeman Real Life Rating Scale (RF) rating scale, Clinical Visual Analogue Scale (cVAS) for eye contact, and VAS for social interaction)
 - language and communication (e.g., language subscale of the RF, cVAS for talkativeness)
 - repetitive behaviour and rituals (e.g., compulsive subscale of the Yale Brown Obsessive Compulsive Scale (YBOCS))
2. Improvement of associated features of ASD, including related psychopathology – aggressive or violent behaviour, self-harm, attention and concentration problems, sleep disturbance, gastrointestinal function, hyperactivity, mood.
3. Overall autistic behaviour, for example, as measured by the following scales:
 - CGI – Clinical Global Impressions
 - RF – Ritvo-Freeman Real Life Rating Scale
 - YBOCS – Obsessive Compulsive Scale
 - cVAS – Clinical Visual Analogue Scale
4. Quality of life questionnaires for individuals with ASD and/or family/carers.
5. Drug safety was reported where it accompanied effectiveness data. This included neurological, autonomic, cardiovascular, psychic and other adverse events and side effects relevant to the safety profile of the drug; for example, weight gain, sedation, extrapyramidal effects, blood pressure, cardiac events, neuroleptic malignant syndrome, liver functioning, seizures.

2.6 LIMITATIONS OF THE REVIEW

This study used a structured approach to review the literature. However, there are some inherent limitations with this approach. Namely, systematic reviews are limited by the quality of the studies included in the review and the review's methodology.

This review was limited by the restriction to English language studies. Restriction by language may result in study bias, but the direction of this bias cannot be determined. In addition, the review has been limited to the published academic literature, and has not appraised unpublished work. Restriction to the published literature is likely to lead to bias since the unpublished literature tends to consist of studies not identifying a significant result.

Papers published pre-1980 were not considered. In 1980, definitions and diagnostic criteria became more consistent with the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association 1980). At this time, autism spectrum disorders were officially recognised as disorders of development, and not of psychoses (Wing 1996a).

The review was limited to studies describing drug interventions involving adolescent and adult patient samples. This focus was determined by the New Zealand Ministry of Health's Disability Services Directorate (DSD), which commissioned the review to inform development of a Best Practice Guideline for people with ASD and their carers. A particular interest of the DSD was on effective services for young people with ASD transitioning to adult services. A further justification for the distinct focus on research relating to adolescents and adults is that autism may qualitatively change with advancing age. Symptoms of autism fluctuate in adolescence and early adulthood compared to childhood, with increasing adaptive skills (including language fluency) in most people in middle

adulthood and later life (Korkmaz 2000). Conversely, psychiatric morbidity, including depression and behavioural problems such as aggression and self-destructive behaviour, can increase in adolescence and adulthood (Korkmaz 2000; Larsen and Mouridsen 1997; Mesibov and Handlan 1997; Rumsey et al. 1985). Different outcome measures may be more relevant to studies involving adolescent and adult participants than those that are commonly used in studies of children. Moreover, variations on symptomatology across the lifespan mean that results of studies of children are not directly transferable to older populations, and vice versa.

Where mean and/or median age was not provided and the age range included adolescents, studies were excluded if they did not report data on adolescents separately from that on children. Supporting this decision rule, it was noted that in studies of broad age ranges where mean/median ages were provided, the samples tended to be loaded with very young children (reporting a mean age commonly around seven years).

Studies were primarily selected for evaluating effectiveness and randomised controlled trials are the ideal study design for this objective. However, due to the relatively rare prevalence of ASD in the community and the practical challenges of conducting RCTs, the sample sizes of such trials in this area are generally small. Small sampled studies tend to lack sufficient statistical power to reliably estimate the risk of side effects, and in particular, rare significant adverse events. (These and other methodological limitations of the evidence base are discussed in **Section 4.2**)

Studies were initially selected for appraisal by examining the articles' abstracts. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full text article. However, where detail was lacking or ambiguous, papers were retrieved as full text to minimise this possibility.

All studies included in this review were conducted outside New Zealand, and therefore, their generalisability to the New Zealand population and context may be limited and needs to be considered. The availability in New Zealand of pharmacological interventions commonly used for ASD is discussed in **Section 1.4**, and details of what medications are used in New Zealand are presented in **Table 2, page 9**. Differences between doses used in included primary studies and usual practice in New Zealand are discussed as part of study appraisal in the Results Section.

This review was confined to an examination of the effectiveness, and safety of the interventions and did not consider the acceptability, or any ethical, economic or legal considerations associated with these interventions.

Although two researchers appraised (different) articles included in this review, they did not systematically cross-validate the appraisal process. However, discussion of complex trial designs for some studies did occur.

The review scope was developed with the assistance of Ministry of Health staff.

This review was conducted over a limited timeframe (February, 2003 – July, 2003).

This review has greatly benefited from the advice and external peer review provided by the expert consultant, Dr Matt Eggleston, as well as by the internal peer reviewer, Dr Ray Kirk. However, it has not been exposed to wider peer review.

For a detailed description of interventions and evaluation methods, and results used in the studies appraised, the reader is referred to the original papers cited.

Chapter 3: Results

3.1 IDENTIFICATION OF ELIGIBLE PAPERS

Of more than 1,500 studies identified by the search strategy, 50 full text articles were retrieved after excluding studies from the search titles, abstracts and reference lists. Of these, 38 did not fulfil the inclusion criteria and were excluded. These are presented in **Appendix 3**, annotated with the specific reason for exclusion.

Reasons for exclusion included the following:

- mean/median age range less than 13 years or results not reported separately for those aged >12 years (n=20)
- sample size less than 10 (n=4)
- not clear that (at least 75% of) patients had ASD (n=2)
- considered fenfluramine – an ineligible drug (n=6)
- considered a drug not designed for therapeutic benefit (n=1)
- were commentaries/narrative reviews, not systematic reviews (n=3)
- were systematic reviews without inclusion criteria overlapping with this review (n=1)
- ineligible study design (open trial without a control group) (n=1).

A total of 12 articles were eligible for inclusion and were fully appraised, consisting of seven papers reporting secondary research (i.e., systematic reviews) and five papers reporting primary research. These included papers are listed in **Appendix 4**.

Other cited publications (e.g., those providing background material) are presented in the **References**.

3.2 SECONDARY RESEARCH

The search strategy identified seven relevant systematic reviews. The methods, conclusions and critical comments relating to each article are described in **Table 4, pages 21-28**, presented in reverse chronological order of publication.

Each review is discussed below under the drug class considered.

Anticonvulsants

Di Martino and Tuchman (2001)

Di Martino and Tuchman's (2001) review examined the evidence on use of antiepileptic (anticonvulsant) drugs in the treatment of autism. The search strategy was very limited with only one database searched. Ten studies were appraised, however none were controlled trials. Whilst the search strategy did attempt to identify studies on adolescents, the studies primarily concerned children (in sum, two adults, and 29 children and adolescents between the ages of 22 months and 14 years).

Intellectual disability was present in 21 of 31 individuals described in these studies and epilepsy in 18 of 31. Only two of the studies used standardised scales for the diagnosis and measurement of symptom severity during treatment. Affective symptoms (mania, hypomania or depression) were found in seven of 31 patients, but only two studies used specific diagnostic criteria for mood disorders. Appraisal and

discussion of the studies was brief. Despite improvements being reported in a variety of domains for several agents, all of the studies were small, uncontrolled and varied methodologically, making them difficult to compare. The authors point out the clear need for randomised trials on the use of anticonvulsants in treating people with autism and epilepsy. It was not clear whether the anticonvulsants investigated were being used to target epilepsy, mood disorders (particularly bipolar disorder), or core autistic symptoms specifically. Managing comorbidities may lead to improvements in core features of autism.

Atypical antipsychotics (e.g., risperidone)

Barnard et al. (2002)

A recent review of the use of atypical antipsychotics in autistic disorder by Barnard et al. (2002) employed a limited search of two databases and handsearching of relevant retrieved papers' bibliographies using inclusive selection criteria. Nineteen studies were appraised, including two double-blind cross-over randomised controlled trials: McDougle et al.'s (1998) trial of risperidone (also appraised in the current review), and a trial of amisulpride by Dolfus et al. (1992) involving nine children (that did not meet the current review's selection criteria). Appraisal and presentation of studies and side effect profiles was thorough and detailed. Most studies (n=13) considered risperidone with a median optimal dose of 2.7 mg/day (range: 0.875 – 7 mg/day). Authors concluded that there was "an indication" that risperidone may be effective in reducing hyperactivity, aggression, and repetitive behaviours, often without inducing severe adverse reactions. Furthermore, olanzapine and quetiapine may be effective, although the review identified little evidence for the effectiveness of amisulpride or quetiapine in people with ASD. The authors called for randomised trials to clarify the effectiveness of these interventions.

Toren et al. (1998)

A review of the use of atypical neuroleptics for children and adolescents, which was not restricted to studies on autism, was conducted by Toren et al. (1998). A limited search of Medline from 1974 to 1998 and selected handsearching identified 62 studies, five of which were placebo-controlled clinical trials. There was limited research related to treatment of PDDs and no studies identified were eligible for the current review. The authors note that small sample sizes, short treatment duration, and the lack of double-blind controlled trials limits the ability to make conclusions about the effectiveness of atypical neuroleptics or risk estimates for adverse events. They also call for systematic research into dose-response and dose-risk relationships for atypical neuroleptics in children.

Secretin

Patel et al. (2002)

Patel et al.'s (2002) review was on the effects of secretin (human and porcine) on behaviour in people with autism. A very limited search utilising only one database was performed. Relevant press releases were also gathered from the Internet, though it was not clear how this search was conducted. Non-English language articles were excluded in this review. No formal appraisal methods were employed and the overall number of articles retrieved and appraised, their characteristics, and which authors appraised them was unclear. Despite the lack of detail regarding the specific methodology of the review, the authors did include a thorough discussion of all of the RCTs (n=8) they identified. Most of the double-blind placebo-controlled studies (n=7) did not report any improvements in behaviour across a number of measures. Some information regarding adverse events was presented in the text, but this was not synthesised. A number of important methodological limitations of the eight studies (particularly relating to their comparability) were also noted. There may have been a positive response bias in interpretation of results because of a lack of an intention-to-treat analysis in many studies. The authors call for further studies on secretin that use a double-blind placebo-controlled design, but advise of the need for these to adopt standardised methods and assessment procedures to enable meaningful conclusions to be drawn.

Vitamins (niacin, vitamin B6)

Nye and Brice (2002)

A systematic review conducted for the Cochrane Collaboration by Nye and Brice (2002) aimed to determine the efficacy of vitamin B6 (pyridoxine) combined with magnesium for treating social, communication and behavioural responses of children and adults with autism. A comprehensive search strategy of studies published to January 2002, involving several databases, handsearching and translation of non-English language articles, was undertaken. Studies were included which were fully randomised placebo-controlled trials involving children or adults with autism with no more than 20 percent subject attrition. Attrition may be significant given that compliance in taking vitamin B6, which is very bitter, is frequently a problem (Rimland 1998). Criteria for assessment of methodological quality and additional analyses were established in advance, and two reviewers independently applied selection criteria.

The review identified two randomised, double-blind placebo-controlled cross-over trials: Tolbert et al. (1993) and Findling et al. (1997). Neither of these met selection criteria for the current review and adverse events were not discussed. The authors concluded that due to the small number of studies, their methodological quality, and small sample sizes, there is no reliable evidence that combined vitamin B6 and magnesium improve the behaviour of children with autism. Suggestions for future research included investigating longer periods of treatment, establishing multi-centre trials to increase sample sizes, and using a broader range of outcome measures, including quality of life, educational readiness, independence, and daily living skills.

Pfeiffer et al. (1995)

An earlier review of the effectiveness of vitamin B6 (pyridoxine) and magnesium in the treatment of autism by Pfeiffer et al. (1995) also included a review of the methodology of studies in the area. There was little information given on search terms or selection criteria employed, or the selection and synthesis process. Initially, articles that did not provide statistical data that would permit meta-analyses were excluded; however, this criteria was removed as it was deemed to be too restrictive. A moderately broad search of three databases and reference list checking identified 12 studies for appraisal. Three studies were translated into the English language from French. No study was identified which met selection criteria for the current review. Criteria for assessment of methodological quality were established in advance and results were presented as a narrative review organised around key methodological features relating to study quality. Study designs, sample size, measures and results were presented in tables, although there was no data presented on baseline participant characteristics, or on adverse events.

Of the 12 studies appraised, two were uncontrolled trials, three were non-randomised controlled trials, and seven were randomised controlled trials. The 10 studies measuring behavioural changes all found moderate to marked improvements, and two reported significant decreases in autistic behaviours. The authors caution that interpretation of these positive findings needs to take into account methodological shortcomings inherent in many studies. These included imprecise outcome measures, small samples, and short-term follow-up. The repeat use of the same participants in multiple studies was also suggested as a possibility given that participants in nearly all studies came from two treatment centres and there was extensive overlap in paper authorship. The authors concluded that combined B6 and magnesium treatment “may be a promising adjunct to the treatment of autism”.

Kleijnen and Knipschild (1991)

A review of the effects of niacin, vitamin B6, and other multivitamins on mental functions was conducted by Kleijnen and Knipschild (1991). The authors considered publications to 1990 from three databases and appraised only those involving parallel group design. Criteria for assessment of methodological quality were established in advance and studies were scored on these as an indication of quality. Of 53 controlled trials identified for appraisal, five were cross-over trials involving children with autism treated with very high doses of vitamin B6 (alone or combined with magnesium). None met selection criteria for the current review. The studies involving autism were generally flawed in terms of criteria relating to sample size, presentation of baseline characteristics, description of changes in concomitant medication or therapy, and presentation of statistical results. There were some positive

findings from the studies relating to autism, but the authors concluded that further evidence is needed before definitive conclusions can be drawn. Across all the trials, gastrointestinal complaints were listed as the most frequently reported adverse effect for vitamin B6, although no data were provided.

Conclusions relevant to secondary research appraised

Seven systematic reviews were appraised. Two reviews employing relatively limited search strategies considered atypical antipsychotics. With respect to 19 studies relevant to autism, including two double-blind RCTs, Barnard et al. (2002) reported that risperidone may be effective in reducing hyperactivity, aggression, and repetitive behaviours. They also reported the possibility that olanzapine and quetiapine may be effective. An earlier review by Toren et al. (1998) identified five placebo-controlled clinical trials but the authors were unable to draw firm conclusions due to methodological limitations of the research considered.

One review employing a very limited search strategy considered the use of antiepileptic drugs in the treatment of autism (Di Martino and Tuchman 2001). Ten uncontrolled studies were appraised and these were primarily concerned with children, often with comorbid epilepsy. Whilst some improvements were reported post-treatment, design limitations and methodological variations mean that there was little robust evidence to support the use of anticonvulsant drugs for managing autism.

Another review, also employing a very limited search of literature, considered the effects of secretin on the clinical management of autism (2002). Of eight RCTs that were identified, most did not report any improvements in behaviour across a number of measures.

Three systematic reviews dealt with vitamin therapy. A high quality Cochrane Collaboration review by Nye and Brice (2002) considered the efficacy of vitamin B6 (pyridoxine) and magnesium for managing autism. Two randomised, placebo-controlled trials were identified; however, due to their methodological quality and small sample sizes, the authors concluded that there was no reliable evidence that these vitamins improve the behaviour of children with autism. Also considering the use of vitamin B6 and magnesium, a review by Pfeiffer et al. (1995), using a less comprehensive search with less rigorous selection criteria, identified 12 studies for appraisal, including seven RCTs. Most studies reported moderate to marked behavioural improvements following treatment, however methodological shortcomings limited confidence in these findings. A third review, published in 1991 considered the effects of niacin, vitamin B6, and other multivitamins on mental functions for a range of patients (Kleijnen and Knipschild 1991). Five cross-over trials involving children with autism treated with very high doses of vitamin B6 alone or with magnesium, reported some positive findings of effectiveness. However, these studies were generally flawed and no conclusions could be drawn.

All studies commented on methodological limitations of pharmacotherapy studies related to managing autism. These included small sample sizes, short treatment duration and follow-up, imprecise outcome measures, and the lack of double-blind controlled trials. Some authors suggested that to improve quality, future trials should standardise methods and assessment procedures. Full reporting of baseline characteristics, changes in concomitant treatment, and presentation of results was also recommended to permit studies to be compared and synthesised.

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
Barnard et al. (2002) UK	<p>Aim To review the use of atypical antipsychotics in autistic disorder.</p> <p>Search: 1966 – June 2000.</p> <p>Databases searched Medline, Web of Science (from 1981).</p> <p>Search terms: 'atypical/novel/new generation antipsychotic', 'antipsychotic', 'amisulpride', 'benzamide', 'clozapine', 'iloperidone', 'olanzapine', 'pipamperone', 'quetiapine', 'risperidone', 'sertindole', 'ziprasidone', 'zotepine', 'autism' and 'autistic'.</p> <p>Reference lists of relevant articles were cross-checked.</p>	<p>No restrictions in study designs considered.</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ none stated. 	<p>Nineteen studies appraised, including two randomised controlled trials (double-blind, cross-over design), and 17 were open trials or prospective case series.</p> <p>Antipsychotics evaluated included risperidone (in 13 studies), olanzapine (3 studies), and single studies of clozapine, amisulpride, and quetiapine.</p> <p>Studies were at least of six weeks duration, and the majority focused on children, especially those involving olanzapine, clozapine, amisulpride, and quetiapine.</p> <p>One study was mainly concerned with measuring cognition but the remaining 19 focused on behavioural outcomes.</p> <p>The two RCTs identified included a trial by McDougle et al. (1998) of risperidone (which is appraised in the current review), and a trial by Dollfus et al. (1992) of amisulpride which included nine children (mean age=9 years).</p> <p>The McDougle et al. study of risperidone found significant overall improvements following treatment, compared to placebo, and this was consistent with findings from several other non-controlled studies that patients responded after taking the drug. Median optimal dose across 13 studies was 2.7 mg/day (range: 0.875 – 7 mg/day).</p> <p>Authors' conclusions There is "an indication" that risperidone may be effective in reducing hyperactivity, aggression, and repetitive behaviours, often without inducing severe adverse reactions. Olanzapine and quetiapine may be effective, though there is little evidence for the effectiveness of amisulpride or quetiapine in this population. Randomised trials are required to clarify the effectiveness of these agents.</p>	<ul style="list-style-type: none"> ▪ inclusive selection criteria, considering studies of patients of all ages, and representing any study design ▪ limited range of databases searched, though handsearching of reference lists would have broadened capture ▪ studies described critically in the text and clear tabular presentation of main features of sample, methods and design quality provided a detailed tabular breakdown of side effects identified across appraised studies by drug is presented ▪ thorough and detailed discussion of results under categories including different core autistic symptoms and related psychopathology, cognition, and side effects ▪ discussion of common assessment measures employed, methodological limitations of the literature, and future directions for research ▪ only one study was identified by Barnard et al. which meets selection criteria for the current review (McDougle et al. 1998).

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
<p>Nye and Brice (2002)</p> <p>USA</p>	<p>Aim To determine the efficacy of vitamin B6 (pyridoxine) and magnesium for treating social, communication and behavioural responses of children and adults with autism. Search: 1861 – January 2002.</p> <p>Databases searched Medline (1966-2002), Cochrane Controlled Trials register, EMBASE (1980-2002), PsychINFO (1887-2002), Dissertation Abstracts International (1861-2002). The search engine FirstSearch was also used. Handsearching was performed on the Journal of Autism and Developmental Disabilities and the reference lists for all retrieved studies and review articles were cross-checked.</p> <p>Search terms Child development disorders – pervasive, speech disorders, autism, pervasive developmental disorder (PDD), language delay, communication disorder, childhood schizophrenia, Kanner, Aspergers, vitamin B6, pyridoxine, magnesium, vitamin B complex, and similar terms.</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ fully randomised, placebo-controlled trials ▪ trials involving children or adults with autism ▪ treatment was combined vitamin B6 with magnesium in tablet or powder form given for between one and 52 weeks ▪ outcome measures included verbal behaviour, non-verbal behaviour, social interaction. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ studies reporting more than 20 percent attrition of participants. 	<p>Two reviewers independently evaluated all potential studies identified by the search strategy and disagreements were resolved by discussion. Data of eligible articles were synthesised and analysed using RevMan 4.1.1.</p> <p>The search strategy identified 58 abstracts: 41 were ineligible due to not being relevant data based studies, 15 were ineligible due to study design (five non-randomised, double-blind cross-over trials, eight open non-randomised trials, two trials using open and double-blind comparison arms), and two were eligible RCTs.</p> <p>The two RCTs eligible for appraisal were both randomised, double-blind, placebo-controlled cross-over trials. One of these by Tolbert et al. (1993) considered 20 children/adolescents aged 6-18 years treated with B6 (200 mg/70kg) and magnesium (100 mg/70kg) for 20 weeks. No difference was reported between treatment and placebo phases. However, the study provided insufficient data (no means or SDs) to conduct a meta-analysis and did not supply supporting data (e.g., of randomisation) when contacted by the review authors.</p> <p>The other study by Findling et al. (1997), considered 10 children (mean age 6 years) treated for four weeks with B6 (30 mg/kg, maximum 1 gram/day) and magnesium (10 mg/kg, maximum 350 mg/day). The study reported no significant differences between treatment and placebo groups on measures of social interaction, communication, compulsivity, impulsivity, or hyperactivity. Only one (of 10) behavioural measures showed a treatment effect at week four.</p> <p>Authors' conclusions Due to the small number of studies, their poor methodological quality, and small sample sizes, there was no reliable evidence that combined vitamin B6 and magnesium improve the behaviour of children with autism. The authors argue that longer treatment periods may affect response and that this may interact with variables such as age, severity, or outcome. The authors suggest that multiple-centre trials would allow aggregation of data that would increase sample sizes and power of the analyses and findings. They also recommend a broader range of outcome measures than solely core features of autism, including quality of life, educational readiness, independence, and daily living skills.</p>	<ul style="list-style-type: none"> ▪ narrowly defined review of RCTs evaluating B6 and magnesium use for treating ASD ▪ clearly defined and specific selection criteria ▪ non-English language articles translated and included ▪ comprehensive search strategy involving extensive database search and handsearching ▪ criteria for assessment of methodological quality were established in advance ▪ brief description and detailed reasons for exclusion of excluded trials was provided ▪ detailed description of appraised studies, including methodological quality, outcomes, measures and results ▪ no mention of adverse events ▪ discussion of study results, methodological limitations of the literature and gaps in research ▪ no study was identified by Nye and Brice which meets selection criteria for the current review.

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
Patel et al. (2002) USA	<p>Aim To assess the effects of secretin on behaviour in all individuals with autism.</p> <p>Search: January 1996 – November 2001.</p> <p>Databases searched Medline (1966-2001); No search terms mentioned.</p> <p>English language articles only. Press releases from the World Wide Web also searched.</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ it was implied that only studies investigating samples meeting criteria for DSM-IV-R autistic disorder were relevant ▪ no restrictions in study designs considered. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ non-English articles. 	<p>Only evidence evaluating secretin's effects on the behaviour of children with autism was identified.</p> <p>The findings of a case series study and an eight week open trial of porcine secretin are discussed. Statistically significant differences between responder and non-responder scores were reported. Higher rates of drop-out occurred among non-responders than responders.</p> <p>Positive findings One double-blind, placebo-controlled RCT of synthetic human secretin in 30 children (2-10 years) with autistic disorder or PDD-NOS was appraised that demonstrated a positive effect. This study used a variety of standard rating scales. Although average scores for all groups improved with time, secretin was more efficacious in those with greater baseline severity and when given as a high dose.</p> <p>In addition, an otherwise unpublished meta-analysis described in a drug-industry sponsored press release of four published studies was described. These studies may be case series but very little information on the studies was provided in the text.</p>	<ul style="list-style-type: none"> ▪ very limited search strategy with no mention of search terms used ▪ selection criteria and methods of the review not clearly defined ▪ rationale for conducting a review related to the extent of interest expressed in the topic by the media ▪ discusses positive and negative studies in some detail ▪ presented an unpublished meta-analysis report from a drug company sponsored press release. Neither the definition of clinical response or the method of pooling results was clearly outlined by the reviewers ▪ of the authors listed it is not clear how many were responsible for reviewing the studies, or whether this was done independently ▪ clinical studies using different forms of secretin (synthetic human and porcine) were not compared and it is unclear whether there are specific differences apart from the known structural difference in amino acid sequences ▪ some information regarding adverse events presented in the text but not synthesised ▪ there was a lack of consistency in the instruments employed to make diagnoses and assessments in social and communication behaviour ▪ no studies were identified by Patel et al. which met selection criteria for the current review.

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
Patel et al. (2002) USA (Continued)			<p>Negative findings Seven RCTs were appraised that examined the effects of secretin on children and did not find it to be effective. The majority of these studies were conducted double-blind and used standardised scales for assessment and measuring outcomes. Overall these studies generally reported few statistically significant differences between groups in most or all outcome measures at follow-up. A variety of adverse effects were reported, though not all of these could be clearly attributed to secretin.</p> <p>For studies with positive findings, it is suggested that there may be a positive response bias in interpretation of results because of the lack of an intention-to-treat analysis. It is noted that the pharmaceutical industry also has had a strong involvement in the early studies of secretin use, particularly those reporting positive findings.</p> <p>Authors' conclusions Well-designed clinical trials evaluating secretin did not produce evidence of beneficial effects. Scant data was found addressing issues around the safety and tolerability of the drug. Further studies that adopt a double-blind, placebo-controlled design, but also use standardised methods and assessments, are required.</p>	

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
Di Martino and Tuchman (2001) Italy/USA	<p>Aim To review the use of antiepileptic drugs in autism spectrum disorders (ASD), particularly where there may be comorbid epilepsy and/or mood disorder.</p> <p>Search: 1994 – 2000.</p> <p>Databases searched Medline.</p> <p>Search terms 'autism', 'anticonvulsant', 'valproic acid', 'carbamazepine', 'lamotrigine', 'gabapentine', 'topiramate', 'vigabatrine', 'mood disorders', 'children', 'adolescents', 'epilepsy', 'behavioral disorders' and 'pervasive developmental disorders (PDD)'. The name of each drug was also associated to the term 'mechanism of action'.</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ only studies that dealt specifically with developmental issues were appraised, although adult studies were cited for continuity and relevance ▪ a DSM-III-R or DSM-IV diagnosis of autism spectrum disorder ▪ no restrictions in study designs considered. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ non-English language articles. 	<p>From 1,000 articles identified by the search strategy, 95 English language articles were selected and narratively reviewed. Authors specifically appraised 10 case reports or open-label studies on antiepileptic drugs in individuals with ASD.</p> <p>Combined, these considered two adults and 29 children and adolescents between the ages of 22 months and 14 years. Diagnoses included infantile autism, PDD, Retts and Aspergers. Mental retardation was present in 21 of 31 individuals described in these studies and epilepsy in 18 of 31.</p> <p>Only two of the studies used standardised scales for the diagnosis and measurement of symptom severity during treatment. An overall improvement in communication skills, both for expressive and comprehensive language, was reported for all eight patients treated with valproic acid (known as sodium valproate in NZ), in eight of 13 treated with lamotrigine, and in two of three treated with carbamazepine. None of the studies used specific language assessment tests. In six of eight patients treated with valproic acid an improvement in socialisation skills was also reported.</p> <p>Affective symptoms (mania, hypomania or depression) were found in seven of 31 patients but only two studies used specific diagnostic criteria for mood disorders.</p> <p>Authors conclusions The evidence supports the hypothesis that there may be a subgroup of children and adolescents with autism and comorbid epilepsy and/or mood disorders that preferentially respond to antiepileptic drugs. However, the data is still very preliminary, and further investigations with double-blind placebo-controlled trials are needed. All of the evidence to date on the effectiveness of the affective antiepileptic drugs on autism with epilepsy is based on case reports and not on controlled clinical trials.</p>	<ul style="list-style-type: none"> ▪ only one database searched, no citation searching ▪ English-language articles only considered ▪ no mention of adverse events (except for one child not tolerating carbamazepine) ▪ very little detail on the appraised studies provided ▪ few studies used standard scales or measures ▪ all studies reviewed had very small samples ▪ of the studies appraised none were controlled ▪ three areas were the focus of a broad discussion: (1) the use of antiepileptics in individuals with ASD; (2) literature on mood disorder in children and adolescents with epilepsy and autism; and (3) hypothesised psychotropic mechanisms of action of affective antiepileptic drugs ▪ no studies were identified by Di Martino and Tuchman that met criteria for the current review. <p>Note: Belsito et al. (2001) subsequently published a RCT on the use of lamotrigine in children with autistic disorder (also excluded from the current review).</p>

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
Toren et al. (1998) Israel	<p>Aim To review clinical experience with atypical neuroleptics in children and adolescents.</p> <p>Search: 1974 – 1998.</p> <p>Databases searched Medline.</p> <p>Search terms 'amisulpride', 'clothiapine', 'clozapine', 'olanzapine', 'remoxipride', 'risperidone', 'sulpiride', 'tiapride', 'children' and 'adolescents'.</p> <p>Handsearching of all issues of the Journal of Child and Adolescent Psychopharmacology was performed, and reference lists of papers were cross-checked.</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ published in the English language ▪ the number of participating children and adolescents were specified separately from adults. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ none stated. 	<p>62 studies identified including five blind placebo-controlled clinical trials, 24 open-label clinical trials, and 33 case series.</p> <p>Studies described use of the following atypical neuroleptics: amisulpride, clothiapine, clozapine, olanzapine, remoxipride, risperidone, sulpiride, tiapride in children and adolescents.</p> <p>Effectiveness is discussed in relation to the treatment of schizophrenia, mood disorders, obsessive-compulsive disorder, Tourette's disorder, and pervasive developmental disorders (PDD). Relevant to PDD, one clinical trial was identified (Dollfus et al. 1992) involving nine children with autism treated with amisulpride, which found beneficial effects.</p> <p>There were some preliminary findings regarding the use of risperidone. In four open trials, 30/40 children/adolescents with PDDs exhibited improvements in interfering behavioural symptoms after treatment with the drug (0.75 - 4.0 mg/day), with the most common side effects being weight gain and sedation.</p> <p>Authors' conclusions Almost all of the studies were open, uncontrolled clinical trials of relatively short-term treatment in small groups of patients. This seriously limits the conclusions that can be drawn. The most convincing evidence for efficacy related to clozapine is in the treatment of schizophrenia whilst data on other atypical neuroleptics in other disorders are still sparse and further research is needed.</p> <p>No estimates of the risk of tardive dyskinesia, neuroleptic malignant syndrome, or other possible side effects. There is a need for systematic dose-response and dose-risk relationships to be established for atypical neuroleptics in children, as lower doses may be required to enable better tolerance and compliance. Extreme caution should be taken in generalising results from the adult to the pediatric population.</p>	<ul style="list-style-type: none"> ▪ broad review of atypical neuroleptics' use generally rather than for treating ASD specifically ▪ inclusive selection criteria representing any study design ▪ very limited range of databases searched, though handsearching of a key journal and reference lists would have broadened capture ▪ studies described critically in the text for each drug and clear tabular presentation of main features of sample, methods and design quality provided ▪ a detailed tabular breakdown of side effects identified across appraised studied by drug is presented ▪ results are also described by disorder treated, including pervasive developmental disorders ▪ discussion of methodological limitations of the literature and gaps in research ▪ no study was identified by Toren et al. which meets selection criteria for the current review.

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
Pfeiffer et al. (1995) USA	<p>Aim To assess the effectiveness of vitamin B6 (Pyroxidine) and magnesium in the treatment of autism, and to review the methodology of studies in the area.</p> <p>Search: 1975 – “present” (no later than 1995).</p> <p>Databases searched MEDLARS, PsychINFO, Mental Health Abstracts.</p> <p>Search terms Not described.</p> <p>Cross-checking was performed of the reference lists for identified eligible studies. Translation of three French studies into English was conducted.</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ trials involving children or adults with autism ▪ treatment was combined vitamin B6 with magnesium. <p>Note that initially articles that did not provide statistical data that would permit meta-analyses were excluded, however this criteria was removed as it excluded most of the literature.</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ none described. 	<p>The search strategy identified 12 studies eligible for appraisal. There was extensive overlap between authorship of these: LeLord contributed to 11, Martineau to six, Barthelemy to 11 and Garreau to nine of the 12 articles. Studies included two uncontrolled trials, three non-randomised controlled trials, and seven randomised controlled trials.</p> <p>Pre-determined criteria for assessment of methodological quality were applied to all studies, and results were presented as a narrative synthesis under nine methodological categories, including time period of administration, dosage, sample size, blind analysis, placebo group, comparison group, follow-up period, random assignment, and instrumentation.</p> <p>Seven of 10 studies reporting analysis of urinary homovanillic acid (UHVA) found decreased levels, and one increased levels. However, the authors comment that this proxy outcome variable may not necessarily reflect changes in dopamine function in the central nervous system. The six studies reporting electrophysiological analysis all found longer latencies and higher amplitudes during treatment. The ten studies measuring behavioural changes all found moderate to marked improvements, and two reported significant decreases in autistic behaviours.</p> <p>Authors' conclusions Whilst the majority of studies reported a positive response to treatment, interpretation of these positive findings needs to be tempered because of methodological shortcomings inherent in many studies. These included imprecise outcome measures, small samples, possible repeat use of the same participants in multiple studies, no adjustment for regression effects in improvement, and short-term follow-up. The authors conclude that combined B6 and magnesium treatment “may be a promising adjunct to the treatment of autism”. They call for future research with longer follow-up, larger samples, and the use of well-standardised outcome measures.</p>	<ul style="list-style-type: none"> ▪ broadly defined review evaluating B6 and magnesium use for treating autism ▪ selection criteria inferred from review aim rather than specifically stated ▪ non-English language articles translated and included ▪ moderately broad search strategy including three databases and reference checking ▪ criteria for assessment of methodological quality were established in advance ▪ results were presented as a brief narrative synthesis according to methodological aspects relating to study quality ▪ three tables also presented details of study design, sample size, measures and results ▪ no data presented on participant baseline characteristics including age, sex, or diagnosis ▪ no mention of adverse events ▪ discussion of study results, methodological limitations of the literature and gaps in research ▪ no study was identified by Pfeiffer et al. which meets selection criteria for the current review.

Table 4. Secondary research appraised relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Aim and search method	Criteria for inclusion and exclusion	Results and authors' conclusions	Comments
<p>Kleijnen and Knipschild (1991)</p> <p>The Netherlands</p>	<p>Aim To review the effects of niacin, vitamin B6 (pyridoxine), and other multivitamins on mental function.</p> <p>Search: 1965 – 1990.</p> <p>Databases searched Medline (1983-1990), psychiatry section of Excerpta Medica (1965-1990), Index Medicus (1965-1990).</p> <p>Search terms 'vitamins' (including B3 and B6), 'nicotinic acid', 'niacin', 'pyridoxine', and 'nicotinamide' (therapeutic use).</p>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ human trials ▪ parallel group design ▪ niacin and vitamin B6 alone or in combination with other vitamins used ▪ correlates of mental state assessed as outcomes. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ where niacin or vitamin B6 (or analogues) combined with pharmaceutical agents assessed. 	<p>Criteria for assessment of methodological quality were established in advance. They included the following nine factors: well described diagnosis and description of symptoms, at least 50 patients per comparator group, pre-stratification (matching) on relevant prognostic factors, randomisation, presentation of relevant baseline characteristics, patients blinded, assessor blinded, effect measurement reproducible, assessment of other treatment/vitamins, detailed presentation of results (e.g., mean, SD, standard error, confidence interval). Studies were scored a point where each criteria is met, or half a point if partially met (e.g., if 25-50 patients in each group). 53 controlled trials were appraised and scored including five cross-over trials involving children with autism treated with vitamin B6 alone (n=2) or combined with magnesium (n=3). The five studies were scored between 4.5 and 5.5 points using the quality criteria.</p> <p>Methodological limitations included that only one partially met the criteria for sample size (n=37), only one gave partial and incomplete presentation of baseline characteristics, none described changes in concomitant treatments (e.g., medication, behaviour therapy), and only one presented detailed results (partially met in another study). Strengths included that most studies gave a full description of diagnoses, all but one were randomised (regarding condition order), all were patient and assessor-blinded, and nearly all used reproducible outcome measures.</p> <p>Outcome measures In the five trials relating to autism, doses ranged from 30 mg/kg to 3000 mg of vitamin B6 for up to 1.5 months, which represents three times the doses employed by appraised trials concerned with other conditions. Three studies found positive effects, and two found none. Over all 53 trials, gastrointestinal complaints were listed as "the most frequently reported adverse effects" for vitamin B6, but no data was provided specifically for studies involving children with autism.</p> <p>Authors' conclusions Virtually all trials had several methodological flaws. In studies of children with autism, some positive results were found with very high doses of vitamin B6 combined with magnesium, but further evidence is needed before definitive conclusions can be drawn. For many other indications there is no adequate support for controlled trials in favour of vitamin supplementation.</p>	<ul style="list-style-type: none"> ▪ broad review of vitamin use in mental functioning generally rather than for treating ASD specifically ▪ clearly defined and specific selection criteria, though the search was not able to consider papers published since 1990 ▪ moderate range of databases searched ▪ criteria for assessment of methodological quality were established in advance and studies scored on these as a guide to quality ▪ studies were briefly described in the text for each condition ▪ tabular presentation of each quality criteria for each study, as well as limited information on sample size, study duration and basic results ▪ no detailed information on age of sample, outcome measures employed, or study's findings ▪ scant information regarding adverse events ▪ discussion of methodological limitations of the literature and gaps in research ▪ no study was identified by Kleijnen and Knipschild which meets selection criteria for the current review.

3.3 PRIMARY RESEARCH: STUDY DESIGNS AND QUALITY

The search identified five eligible primary research studies. Below is an overview of the study designs and aspects of quality of these studies.

Study design

All five studies were graded as Level 2 evidence according to the NHMRC Scale (see **Appendix 2**) and involved placebo control arms and randomisation procedures. Two studies were randomised controlled trials comparing placebo and intervention conditions over 12 weeks (McDougle et al. 1998; McDougle et al. 1996b). In another RCT (Remington et al. 2001), patients were entered into each of three seven week trials representing varied order of treatment and placebo phases according to a “Latin square” design. Willemsen-Swinkels et al. (1995) conducted two consecutive trials on the same sample. The first was an RCT of a single, moderate dose of the intervention drug, followed a week later by a cross-over RCT involving four weeks of a fixed dose drug or placebo. Finally, a randomised controlled cross-over trial by Zarcone et al. (2001) involved a placebo phase, followed by two separate six week treatment phases at high-dose and low-dose (randomised order), followed by a final placebo phase.

All five studies were double-blind, although in one trial (Zarcone et al. 2001) there was a possible compromise to blind assessment of outcomes by assessor knowledge of the order of placebo and treatment phases. However, assessors were blind to the length of each phase which varied randomly from three to five weeks.

Interventions

Treatments investigated compared with placebo included risperidone (McDougle et al. 1998; Zarcone et al. 2001), the opioid antagonist naltrexone hydrochloride (Willemsen-Swinkels et al. 1995), and fluvoxamine (McDougle et al. 1996b). Remington et al. (2001) was the only study to compare interventions from different drug classes; namely clomipramine and haloperidol.

Intervention drugs were usually commenced at a low dose and then individually titrated upwards, as tolerated, using a preset regimen of increments to a maximum dose (McDougle et al. 1998; McDougle et al. 1996b; Remington et al. 2001; Zarcone et al. 2001). In Zarcone et al.’s (2001) study, there were two dose conditions, low and high-dose, with varying initial doses which were titrated upwards as tolerated, without a maximum dose prescribed. For these four studies, doses therefore varied between study participants based on individual tolerance to the treatment.

Willemsen-Swinkels et al. (1995) employed a set dose regimen of naltrexone beginning with a single, moderate dose versus placebo, followed by a separate trial employing a fixed daily dose of 50mg which was increased to 150mg/day for the second half of the sample due to initial lack of therapeutic effect.

Samples

Total study sample sizes ranged from 20 to 37 participants and averaged 30.2 across the five appraised studies. Participants were recruited from a range of sources including psychiatric hospital or clinic inpatients and outpatients, and in two studies, a mixture of inpatients and outpatients from the same mental health research unit (McDougle et al. 1998; McDougle et al. 1996b).

Three studies concerned adults and the mean age ranged from 28 to 30 years (McDougle et al. 1998; McDougle et al. 1996b; Willemsen-Swinkels et al. 1995). The other two studies considered children, adolescents and adults, with 75 percent of the sample aged over 12 years in one study (Zarcone et al. 2001) and a mean age of 16 years in the other (Remington et al. 2001). In four of the studies, the populations were predominantly male (ranging from 73% to 90%), whilst in one study half of the sample were female (Zarcone et al. 2001).

Study samples consisted predominantly or totally of people with ASD, although self-injurious behaviour (SIB) and aggression were common in all (Zarcone et al. 2001), or large proportions of the samples (Willemsen-Swinkels et al. 1995). Only one study gave detailed information on participants' physical and psychiatric comorbidities (Zarcone et al. 2001).

Outcomes

All studies used standardised scales for measures of effectiveness, including clinician/staff ratings of global behavioural improvement, and ratings of specific behavioural dimensions such as aggression and repetitive behaviour. Mood states and other specific symptoms of autism were sometimes measured. In one study, direct observation of a subsample of patients was included (Willemsen-Swinkels et al. 1995).

Adverse events relevant to the pharmacological intervention were measured, either informally through active or systematic questioning, or through published rating scales. Physical/physiological outcomes varied widely depending on the safety profile of the treatment under investigation. Outcomes included weight change, blood pressure, pulse and temperature measurements, ECG/cardiac monitoring, and in one study, the measurement of liver functioning and plasma β -endorphin and plasma cortisol levels (Willemsen-Swinkels et al. 1995).

3.4 PRIMARY RESEARCH: STUDY RESULTS

Studies are discussed under each drug group below. Full details of each appraised study, including methods, key results, and study strengths and limitations, are provided in evidence **Table 5, pages 35-48** (studies are presented in reverse chronological order of publication, and within the same year, alphabetically by first author).

Studies of risperidone

Two studies, both conducted in the United States of America, considered the use of orally administered risperidone compared to placebo (McDougle et al. 1998; Zarcone et al. 2001). These are discussed below.

McDougle et al. (1998)

McDougle et al. (1998) considered outpatients and inpatients of a mental health research unit in a double-blind, randomised controlled trial (RCT) of 12 weeks duration. Participants were 31 adults (mean age=28 years, 73% male) with autism (55%) or PDD NOS (45%), half of whom were non or minimally verbal. No information on comorbidities was given.

Patients were “drug-free” prior to commencement of the trial, and patients in drug and placebo conditions were similar in baseline characteristics. The risperidone dose of 1 mg/day was gradually increased to 10 mg/day, as individually tolerated (over a period of five weeks), over a period of five weeks (mean daily dose=2.9 mg). Daily doses of 2 to 4 mg would be considered usual practice in New Zealand, although doses greater than 6 to 9 mg/day would be extremely unusual and a target of 10 mg/day seems very high. Outcome measures for effectiveness included clinician ratings on standardised scales for global improvement, repetitive behaviour, aggression, overall symptoms of autism, and ten visual analogue scales measuring various mood states. Adverse events were monitored through a range of blood, temperature and weight measurements and participants were “systematically” examined for extrapyramidal and other adverse events at the four weekly assessments.

Only 77 percent of patients completed the full 12-week trial. However, results from 30 participants who completed at least four of the 12 weeks of the trial were analysed on an intention-to-treat basis. Of the 14 participants receiving risperidone, 57 percent “responded”, according to the CGI measuring global improvement, whilst none did of those who were receiving placebo treatment. Moreover, those receiving risperidone exhibited decreases in aggression, self-injury, repetitive behaviours, motor-

hyperactivity and some mood states (anxiety or nervousness, depression and irritability), as well as improved overall behavioural symptoms of autism, sensorimotor behaviour and affectual reactions. However, there were no changes in sensory responses, social functioning, language outcomes, or the following features: “calm”, “eye contact”, “happy”, “restless”, “social interaction”, “talkative”, and “tired”.

One patient was withdrawn from risperidone treatment due to abnormal gait. Most patients receiving the drug (87%) had at least one adverse event, and each event occurred for no more than one or two individuals, although sedation was observed for nearly half (described as generally mild and transient). This compared with adverse events being observed for 31 percent of those receiving placebo (all experiencing agitation).

Results suggest that at least half of the sample had a positive response to treatment with risperidone. The large number of tests (without adjustment to p values using Bonferroni’s Correction) suggests that some test findings may have been by chance. However, there appeared to be reasonably consistent improvement apparent in behavioural symptoms associated with autism. Improvements were less evident for communicative outcomes and mood states.

Zarcone et al. (2001)

The double-blind, randomised controlled cross-over trial of Zarcone et al. (2001) considered 20 people with developmental disabilities who were outpatients from a psychiatric clinic. Patients all had some degree of intellectual disability, and had exhibited severe self-injurious behaviour, aggression, property destruction or stereotypy for at least six months. Half of the sample were male. Three-quarters were aged over 12 years: five were children aged six to 12 years, six were adolescents aged 13 to 18 years, and nine were adults aged 19 to 65 years. Three-quarters of the sample had autism, 10 percent had PDD NOS, and there was a wide range of other diagnoses and comorbidities present among the sample, including Intermittent Explosive Disorder (IED), Obsessive-Compulsive Disorder, Bipolar Disorder, Attention Deficit Disorder, and Tourette’s Disorder.

The trial consisted of a low-dose and a high-dose treatment phase, the order of which was randomised within each age group, taking place between two placebo phases. The placebo phases varied randomly from three to five weeks in duration, whilst each treatment phase included two weeks of dose titration followed by four weeks at a constant dose. The low dose began at 1 mg/day for children/adolescents and 2 mg/day for adults, titrated up or down as tolerated and held constant for four weeks. High-dose was initially 0.06 mg/kg/day but was decreased to 0.05 mg/kg/day for all adolescents and most adults. Overall, the mean daily dose was 1.8 mg/day for children/adolescents, and 3.5 mg/day for adults. Doses used are consistent with usual practice in New Zealand. Outcome measures included weekly caregiver ratings of standardised scales for behaviour, aggression, and neuroleptic side effects, and biweekly clinician ratings of global behavioural improvement, symptoms of tardive dyskinesia, and weight measurements.

Results were combined across age groups and so cannot be reported specifically for those aged over 12 years, though they made up 75 percent of the sample. Of 20 participants completing at least one six week dose phase, 50 percent “responded” with at least a 50 percent reduction in mean total scores on the Aberrant Behaviour Scale (ABC), and 95 percent showed at least a 25 percent reduction. Patients had lower scores when receiving risperidone than during the initial placebo phase regardless of dose. Whilst patients, clinicians and caregivers were blind to treatment, they were not blind to the general plan of the study – i.e., that there would be initial and post-treatment placebo phases of variable length. Therefore, those making assessments were aware that patients mid-trial were more likely to be in a treatment phase.

A large proportion (84%) of the sample experienced weight gain (on average, 4 kilograms for adolescents and 2.5 kilograms for adults over the 22 week trial), and half experienced sedation in at least one dose phase. The authors acknowledged that reductions in aberrant behaviour may have been confounded with effects of sedation, but argue that other measures of improvement suggest sedation was not debilitating.

No consistent dose effect was evident, which may have been confounded by a reduction of dose for five patients in the high-dose phase due to sedation. ABC scores were lower/improved when in the

second phase of treatment regardless of dose, a finding complicated by a difference at baseline between each dose-order sequence. This may be due to patient's gradual improvement over time whilst receiving the two dose phases.

Summary

The study by McDougle and colleagues (McDougle et al. 1998) involved a somewhat larger sample (n=30 in analyses) than that by Zarcone et al. (2001). However, Zarcone et al.'s cross-over trial meant that all 20 participants received treatment, and comparisons between treatment and placebo conditions were of identical samples. A drawback of this trial was that there was a possible compromise to blind assessment by knowledge of the order of placebo and treatment phases, although this was partially disguised by varying length of placebo phases. McDougle et al.'s (1998) study had a follow-up period of 12 weeks, whilst Zarcone et al.'s (2001) 12 weeks of treatment consisting of two consecutive six week treatment phases (four weeks at a constant dose), one for each high-dose and low-dose phase. Whilst samples were similar in these studies in terms of diagnosis, participants in McDougle's study (1998) were all adults, whereas Zarcone's (2001) sample ranged from six to 65 years and all had exhibited severe self-injurious or aggressive behaviour. Despite these differences, both studies categorised half their participants receiving treatment as "responders" as determined by different measures of global improvement.

McDougle and colleagues (1998) also reported improvements in repetitive behaviours, aggression, self-injury, motor-hyperactivity and some mood states (depression, irritability and nervousness), though not on social functioning or language outcomes. Adverse events/side effects were generally mild or manageable with sedation apparent in half of each study's sample, and weight gain common for most of treatment patients in Zarcone et al.'s (2001) study. In the latter study, there was minimal titration during the trial with distinct high-dose and low-dose phases. The lack of a dose effect in Zarcone et al.'s (2001) study may be because optimal effectiveness is dependent on the individual, requiring titration to individually tolerated dose as was done in McDougle et al.'s (1998) study. Overall, there appears to be preliminary evidence that risperidone may be effective in reducing behavioural problems associated with autism, especially with respect to aggression, repetitive behaviour and hyperactivity, though not with respect to social functioning and language. The drug was well tolerated. Side effects, notably sedation and weight gain, appeared to be common although few people withdrew from these trials due to unmanageable adverse events. It is noted that the treatment period of 12 weeks was relatively brief.

Studies of naltrexone hydrochloride

Willemsen-Swinkels et al. (1995)

One study from The Netherlands (Willemsen-Swinkels et al. 1995) considered the opioid antagonist naltrexone hydrochloride as an oral intervention compared with placebo. The sample were 33 adult institutional residents (mean age: 29 years, 82% male) with mild to profound intellectual disability and self-injurious behaviour either with (73%) or without (27%) autism.

The short-term effectiveness of a single moderate dose of 100 mg/day naltrexone was considered in a double-blind RCT, followed by a double-blind cross-over RCT involving four weeks of treatment involving naltrexone at a daily dose of 50 mg, or placebo. This was increased to 150 mg/day for the second half of the sample due to a lack of therapeutic effect for the first 19 participants.

Effectiveness measures included: staff ratings using standardised questionnaires of aberrant behaviour and global behavioural improvement, a checklist of target behaviours, and direct observations of a subsample of patients (11 participants receiving the low-dose drug). Safety was measured through "active questioning" regarding adverse events, liver functioning tests, and measurement of plasma β -endorphin and plasma cortisol levels.

There were no significant changes to effectiveness outcomes relating to behavioural features of autism or self-injurious behaviour as a result of the single dose of naltrexone, or either the four week trials of low or high-dose naltrexone. A single exception was that stereotyped movements unexpectedly increased independently of drug dose or the diagnosis of the participant, though given the large number

of tests performed this may have been a chance effect. The lack of therapeutic effect was independent of the age or sex of participants, level of intellectual disability, sensitivity to pain, or whether participants were receiving any additional medication. Staff ratings of global improvement revealed that the placebo was more beneficial than low-dose naltrexone for 12 of 16 patients, and improvement was the same for patients receiving placebo as those receiving high-dose naltrexone.

Notable adverse events included one woman who exhibited a severe increase of self-injurious behaviour following low-dose naltrexone, and four participants who experienced sedation or nausea.

Summary

This fully randomised study suggests that naltrexone hydrochloride is ineffective in reducing potentially problematic behavioural features of autism and self-injurious behaviour. Limitations of the study include its small sample, and the ad hoc change to study design relating to dose. The trial period of four weeks was relatively short, and doses were fixed. Doses which were titrated on an individual basis and were administered over a longer period may have led to greater effects; however, the complete absence of any beneficial effect and possible negative effects suggest this is unlikely.

Studies of fluvoxamine

McDougle et al. (1996)

McDougle et al. (1996b) considered inpatients and outpatients of a mental health research unit in a double-blind, randomised controlled trial (RCT) of 12 weeks of treatment using the SSRI fluvoxamine. Participants were 30 adults (mean age=30 years, 90% male) with autism, 13 percent of whom were non or minimally verbal. No information on comorbidities was given.

Patients were drug-free prior to the commencement of the trial, and patients were similar in baseline characteristics. The fluvoxamine dose of 50 mg/day was gradually increased to 300 mg/day, as individually tolerated, over a period of three weeks (mean daily dose=276.7 mg). Outcome measures for effectiveness included clinician ratings on standardised scales for global improvement, repetitive behaviour, aggression, overall symptoms of autism, and maladaptive behaviour. Adverse events were monitored and changes in blood pressure, pulse and ECG recorded. Participants were assessed for anticholinergic and other potential side effects.

All of the patients completed the full 12 week trial and were included in the efficacy analysis. Of the 15 patients receiving fluvoxamine, 53 percent “responded” according to the CGI, whilst none did of those receiving placebo treatment. Moreover, those receiving fluvoxamine exhibited statistically significant decreases in repetitive thoughts, repetitive behaviours, maladaptive behaviours and aggression. An overall improvement in the behavioural symptoms of autism was observed, including improved language usage; however, there were no changes in sensorimotor behaviours, sensory responses, social relationship to people and affectual reactions.

No medically significant adverse events were reported in the fluvoxamine group and only minor side effects were reported in both the treatment and placebo groups.

Summary

This was a well-conducted, fully randomised study, which suggests a positive response to treatment with fluvoxamine in a variety of domains, notably including language usage. Fluvoxamine did not appear to influence “affect” or the way in which individuals with autism related to people. It was also the only study identified to look systematically at the efficacy of an SSRI drug for autism. Limitations of the study include a relatively short follow-up period of 12 weeks, and the lack of details regarding patients’ previous use of psychotropic drugs. As discussed in **Section 2.4**, fluvoxamine is not currently available in New Zealand.

Study comparing haloperidol and clomipramine

Remington et al. (2002)

The double-blind, randomised controlled trial of Remington et al. (2001) considered 37 patients with autism who were being treated in a specialist clinic located in a teaching hospital. Among those who participated (36/37), the majority were male (83%), all had DSM-IV defined autistic disorder, and their ages ranged from 10 to 36 year (mean age=16.3 years). Thirteen of the sample were children aged six to 12 years, 14 were adolescents aged 13 to 18 years and nine were aged 19 to 36 years.

The trial investigated the short-term effectiveness of two interventions, clomipramine and haloperidol. Patients were entered into each of three trials representing varied order of treatment and placebo phases according to a Latin square design (clomipramine-placebo-haloperidol, placebo-haloperidol-clomipramine, haloperidol-clomipramine-placebo). Within each trial, each drug or placebo phase was of seven weeks duration with a one-week placebo washout before and between each phase. Dosage was titrated upwards using a preset regimen of increments (to 50 mg of clomipramine twice a day, and to 0.5 mg of haloperidol twice a day) but further increases were permitted, based on tolerance and clinical assessment. Mean daily dose for clomipramine:128.4 mg (range 100-150 mg), and for haloperidol: 1.3 mg (range 1.0-1.5 mg). In New Zealand, 150 mg is considered a reasonable target dose for clomipramine. Medication could be reduced to the next lowest level if warranted due to suspected side effects.

Effectiveness measures included clinician ratings of overall efficacy and an assessment of scores of a variety of behavioural dimensions. Several scales were used to examine issues of safety and tolerability. Cardiac monitoring was also performed at approximately six week intervals. The level of premature discontinuation due to side effects was higher for those treated with clomipramine compared with those treated with placebo and haloperidol, which influenced subsequent analyses performed.

In intention-to-treat analyses, there were reductions in the overall severity of symptoms as well as specific reductions in irritability and hyperactivity for patients whilst being treated with haloperidol compared with placebo. Similar reductions were not reported for patients receiving clomipramine. When only data from completed trials were compared, improvements were noted for patients receiving haloperidol or clomipramine compared with baseline. However, there were no changes in stereotyped movements, lethargy or inappropriate speech observed in relation to treatment.

No significant adverse events were observed. There were no significant differences between placebo and treatment conditions on scales evaluating extrapyramidal events or side effects, and no significant differences between treatment groups. The most common side effects were fatigue and lethargy.

Summary

In the intention-to-treat sample, haloperidol was more effective than clomipramine in the management of autistic disorder. In a re-analysis of trial completers only, the two agents demonstrated similar improvement when each was compared with baseline. However, there may be a positive response bias in the second analysis because of a lack of an intent-to-treat approach. Notably, clomipramine as well as haloperidol would appear to have been relatively well tolerated with no significant differences between treatment and placebo conditions in EPS or side effects (measured by scales). The duration of the trials was relatively short. A further limitation of the study was that significantly fewer individuals treated with clomipramine were able to complete trial phases for reasons including lack of efficacy. However, the mean daily dose of 128 mg is relatively low compared to what is considered to be usual practice in New Zealand, where 150 mg is considered a reasonable target dose with further increases as tolerated/indicated.

Table 5. Primary research studies appraised relating to the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder.

Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
Remington et al. (2001) Canada NOTE: see key at the end of the entire table for definitions of acronyms and abbreviations	Evidence level: II Study design RCT (cross-over trial). Interventions Clomipramine Haloperidol Comparison Placebo Study setting The Autism and Pervasive Developmental Disorder Clinic, part of a teaching hospital associated with the University of Toronto.	Participants N=36/37 (97.3%) individuals with autistic disorder completed the study. Sample characteristics Sex: 83.3% male Age (mean): 16.3 years Age range: 10-36 years Diagnosis 100% with autistic disorder Inclusion criteria <ul style="list-style-type: none"> ▪ diagnosed as having autistic disorder based on DSM-IV criteria ▪ a recommendation based on initial assessment of pharmacotherapy ▪ evidence that haloperidol or clomipramine had not been used previously ▪ parent or legal guardian provided written informed consent. 	Patients were entered into each of three trials representing varied order of treatment and placebo phases according to a "Latin square" design (clomipramine-placebo-haloperidol, placebo-haloperidol-clomipramine, haloperidol-clomipramine-placebo). Each phase (drug or placebo) lasted up to seven weeks in each trial. A one week placebo washout was carried out before and between each trial. Results across the three trials were combined. Dosage For clomipramine: dose increases were 25 mg at bedtime for 2 days, 25 mg twice a day for 2 days, 25 mg three times a day for 2 days, and 50 mg twice a day, thereafter doses were increased every 3 or 4 days on the basis of clinical assessment. Mean daily dose: 128.4 mg (range 100-150 mg). For haloperidol: the dose increments were 0.25 mg at bedtime for 2 days, 0.25 mg twice a day for 2 days, and 0.5 mg twice a day; thereafter, haloperidol doses were increased in 0.5 mg increments every 3 or 4 days as clinically indicated. Mean daily dose: 1.3 mg (range 1.0-1.5 mg).	Outcome measures Clinician ratings were obtained using: <ul style="list-style-type: none"> ▪ the Childhood Autism Rating Scale (CARS) as a measure of overall behavioural improvement ▪ the Aberrant Behavior Checklist (ABC) provided scores on a variety of dimensions, including stereotypic behaviour. Adverse events/side effects were assessed using: <ul style="list-style-type: none"> ▪ the Dosage Treatment Emergent Symptom Scale (DOTES) as a global measure of side effects ▪ the Extrapyramidal Symptom Rating Scale (ESRS) to specifically evaluate drug-induced EPS. Data analysis Two approaches were used: <ol style="list-style-type: none"> 1. intention-to-treat, this included all subjects who completed at least one week of medication 2. all who had completed a particular treatment arm. 	Effectiveness Of 37 patients recruited, 36 were included in the analysis. In the intent-to-treat sample, significant differences were found for: <ul style="list-style-type: none"> ▪ severity of autistic symptoms on the CARS between groups and baseline ($F_{3,91}=2.70$, $p<0.05$), haloperidol and baseline (post hoc, $p<0.05$), but not for other groups ▪ irritability on the ABC ($F_{3,95}=3.21$, $p<0.05$), haloperidol and baseline (post hoc, $p<0.05$), but not other groups ▪ hyperactivity on the ABC ($F_{3,95}=3.74$, $p=0.01$), haloperidol and baseline (post hoc, $p<0.05$), but not other groups ▪ no differences were detected for stereotypic behaviour, lethargy, or inappropriate speech. 	Comments <ul style="list-style-type: none"> ▪ sample fully randomised ▪ clinician blinded ▪ patient blinded ▪ no information provided on baseline differences (except gender) that would allow assessment of the similarity of samples in each condition ▪ no adjustment to p value for multiple tests (i.e., some effects may be by chance) ▪ although there are benefits in evaluating different interventions in the same individual, the use of a cross-over design may introduce a potential carry over effect when medications of this sort are used in sequence with a short washout interval (one week) ▪ In re-analyses where only those completing the trials were considered, there may be a positive response bias because of the lack of an intent-to-treat analysis.

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Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
Remington et al. (2001) Canada (Continued)		<p>Exclusion criteria</p> <ul style="list-style-type: none"> none mentioned. <p>Additional screening included routine laboratory evaluations and a physical examination.</p> <p>An estimate of intelligence for each individual was undertaken, along with a review of formal psychological testing and a developmental screen (Alpern, Boll, and Shearer Developmental Profile).</p>	<p>A reduction to the next lowest dose was permitted, if warranted on the basis of side effects. Benztropine, an antiparkinsonian medication was allowed if required for side effects. No other psychotropic medications were permitted during the study.</p> <p>Blinding Medications were packaged in similar capsules to maintain the double-blind component, with an equal number of capsules administered across each treatment. Patients and clinicians were blind to treatment used.</p> <p>Timing of assessment The final clinical evaluation for each trial was carried out at week six.</p>	<p>Repeated measures univariate analyses of variance were used to compare placebo, clomipramine, and haloperidol versus baseline. Post-hoc comparisons using Scheffé's F procedure were used where applicable.</p> <p>Safety Cardiac monitoring or a 12-lead ECG was carried out at baseline and during week 6 of each intervention. No significant changes were noted in PR interval, QRS duration, and corrected QT interval. No clinically significant arrhythmias were noted.</p>	<p>In a re-analysis of only completed trials, the following significant differences were reported:</p> <ul style="list-style-type: none"> both haloperidol ($F_{3,33}=4.79$, $p=0.05$) and clomipramine ($F_{3,33}=8.31$, $p<0.05$) proved superior to baseline on the CARS a similar re-evaluation of the ABC scales indicated clomipramine ($F_{3,36}=5.33$, $p<0.05$), as well as haloperidol ($F_{3,36}=10.03$, $p=0.01$) improved scores on irritability versus baseline, and both were superior to baseline on stereotypy ($F_{3,36}=13.95$, $p=0.001$ and $F_{3,36}=8.72$, $p=0.01$, respectively) the placebo group was not superior to baseline on any measures. 	<ul style="list-style-type: none"> overall, the average length of each trial was relatively short at five to six weeks relatively small sample reduced statistical power, especially to identify adverse events.

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Remington et al. (2001) Canada (Continued)			<p>Measures were taken at:</p> <ul style="list-style-type: none"> ▪ baseline, and ▪ every 2 weeks throughout the course of the study. <p>Retention The mean duration across trials for placebo, clomipramine, and haloperidol was 5.4, 4.5, and 5.8 weeks respectively. The level of premature discontinuation was highest in the clomipramine (20/32) group compared with the placebo (11/32) and haloperidol (10/33) groups.</p>		<p>Adverse events Significantly fewer individuals completed full therapeutic trials of clomipramine ($p < 0.001$) compared with haloperidol (37.5% vs 69.7%). Reasons for premature discontinuation can be summarised as: side effects (40%), efficacy – i.e., behavioural problems (40%) and combined efficacy and side effects (20%). Results were non-significant for all ESRS measures and DOTES subscales.</p> <p>Authors' conclusions Haloperidol was more effective than clomipramine in the treatment of autistic disorder. The two agents demonstrated comparable improvement when compared with baseline if there was a full therapeutic trial; however, significantly fewer individuals treated with clomipramine were able to do this, for reasons relating both to side effects and efficacy.</p>	<ul style="list-style-type: none"> ▪ results may be confounded by failing to identify comorbid obsessive compulsive disorder, as this may respond differentially to serotonergic agents), however standardised instruments that would enable this are yet to be developed.

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Zarccone et al. (2001) USA	Evidence level: II Study design RCT (cross-over trial) Intervention Risperidone Comparison Placebo Study setting Outpatients of a psychiatric clinic for the treatment of aggressive, self-injurious, and destructive behaviour. Referred by case manager, family member or teacher.	Participants N=20 people with developmental disabilities. Sample characteristics Sex: 50% male Five participants aged 6-12 years (25%), six aged 13-18 years (30%), nine aged 19-65 years (45%), therefore 75% (n=15) aged 13 years or over. Age range: 6-65 years Ethnicity: 18 Caucasian, one African-American, one Hispanic. Diagnosis (multiple response) 75% with autism, 10% with PDD NOS, 35% with Intermittent Explosive Disorder (IED), 30% with Obsessive-Compulsive Disorder, 25% with Bipolar Affective Disorder, 20% with Attention Deficit Disorder, 15% with Tourette's Disorder. Residence: family home (55%), community home (45%). Level of retardation Mild (10%), moderate (40%), severe (25%), profound (25%). Previous medication Anticonvulsants (35%), antidepressants (25%), stimulants (10%), antipsychotics (5%), none (35%).	The trial included an initial placebo phase (varying between three and five weeks long), high- and low-dose phase (varied order) of up to six weeks, and a second placebo phase (varying between three and five weeks long). Patients within each children/adolescent (n=11) and adult (n=9) group were randomised as to whether they received the high or low-dose phase first, and the length of placebo phase. A non-randomly identified subsample of five patients received naturalistic observation (results of which are not reported here). Also not reported are the results of a six-month open "maintenance" phase of open-label treatment which followed the 22 weeks trial. Dosage and route of transmission Patients were drug-free for two to four weeks before the start of the trial. The actual dosage of risperidone (given orally) was titrated up or down in weekly increments over a two-week period between phases. Each dose was then held constant for four weeks, during which outcomes were measured.	Outcome measures Caregiver ratings of the following: 1. Aberrant Behaviour Checklist – Community (ABC-C). 2. Nisonger Child Behaviour Rating Form (for those aged 6-18 years) or the Self-Injurious Behaviour Questionnaire (SIB-Q) to rate aggression (for those aged over 18 years). Clinician ratings of Clinical Global Impressions (CGI) to rate overall global improvement. Adverse events Clinicians completed the Dyskinesia Identification System: Condensed User Scale (to assess symptoms of tardive dyskinesia) biweekly. Caregivers completed the Neuroleptic Side Effects Checklist. Participants were weighed at each visit.	Effectiveness Of 20 patients receiving risperidone, 10 (50%) "responded" according to 50% reduction in mean ABC-C total scores from initial placebo to optimal dose (and 95% presented at least a 25% reduction in mean ABC-C total scores). Placebo effect observed compared with baseline assessments. When receiving risperidone, patients had lower ABC-C total scores than during the initial placebo phase in both dose sequence groups (low-high: $p < 0.0001$, high-low: $p < 0.0001$). There was not a significant dose effect for the order of drug phases; lower (improved) ABC-C scores occurred in the second phase of the dose sequence regardless of which dose it was (from 28.70 – 23.65 for low-high dose sequence, and from 51.47 – 43.50 for the high-low sequence).	Comments <ul style="list-style-type: none"> ▪ sample randomised ▪ patient blinded ▪ clinicians and caregivers making assessment were not blinded to the general plan of the study, i.e., that there would be initial and post-treatment placebo phases of variable length. This may have led to biased assessments in the central part of the trial when treatment was known to be likely ▪ unusually high proportion of sample also had IED ▪ patients in the high-low dose sequence had higher baseline scores in the ABC-C than those in the low-high dose sequence (92.10 c.f. 63.69), making the analyses comparing sequence groups difficult to interpret. The lack of a clear dose effect may also be because doses were reduced in response to sedation for five patients during the high-dose phase of treatment ▪ well validated outcome and adverse event measures.

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Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
Zarcone et al. (2001) USA (Continued)		<p>Diagnosis based on psychiatric evaluation by a board-certified psychiatrist specialising in developmental disorders.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ mental retardation (IQ < 70) ▪ severe self-injurious behaviour, aggression, property destruction or stereotypy for at least six months ▪ baseline subscale scores on the Aberrant Behaviour Checklist – Community (ABC-C) above the norm for age, gender and setting ▪ age six to 65 years ▪ living in appropriate rehabilitative environment ▪ caregiver willing to dispense medication, complete questionnaires and attend study visits ▪ provision of informed consent from parent or legal guardian (and assent from participant where possible). 	<p>Low-dose was 1 mg/day for children/adolescents and 2 mg/day for adults; high-dose was 0.06 mg/kg/day for the first seven children and three adults, but this was then modified to 0.05 mg/kg/day.</p> <p>Daily dose for children and adolescents (mean; range): 1.8 mg/day; 1.0-2.6 mg/day.</p> <p>Daily dose for adults (mean; range): 3.5 mg/day; 2.5-4.5 mg/day.</p> <p>Blinding Risperidone was mixed with a dilution of placebo to make up the appropriate dose per ml. Patients, caregivers administering drug and clinicians/caregivers rating outcomes were all blinded to treatment used.</p>	<p>Statistics Percentage change from initial placebo phase was calculated for high-dose and low-dose treatment phases (excluding titration weeks) across participants for each outcome measure.</p> <p>A General Linear Mixed (GLM) model (for 20 completers of both treatment phases) to assess the presence of drug, dose or sequence (high-dose, low-dose order) effects based on the ABC-C total score.</p>	<p>Results given for other measures showed variability in strength of improvement between low and high-dose regimen.</p> <p>Safety There was a significant increase in two side effects for those receiving risperidone: 84% of patients experienced weight gain, and 50% experienced sedation in at least one phase (although this is recorded as 40% in the abstract). Children and adolescents gained a mean of 4 kg (range: 1.4 – 9.5 kg) during treatment, and adults gained a mean of 2.5 kg (range: 0 – 10.9 kg). There was no evidence of tardive dyskinesia. No detail on commencement or duration of these side effects but sedation was fairly significant in five cases, leading to dose reductions.</p>	<ul style="list-style-type: none"> ▪ no reason given for drop-out of two patients for one of the two treatment phases (high or low-dose) ▪ relatively small sample reducing ability to identify adverse events, although cross-over design increases validity and generalisability of conclusions ▪ dosage per kilogram for the high-dose phase was altered during the trial (no explanation given) ▪ the maintenance phase was an open trial and therefore results are ineligible for reporting ▪ results not reported separately for children and those aged over 12 years ▪ no adjustment to p value for multiple tests (i.e., some effects may be by chance).

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Zarcone et al. (2001) USA (Continued)		Exclusion criteria <ul style="list-style-type: none"> ▪ uncontrolled seizures over past two years ▪ acute illness ▪ living in "pathogenic" environment ▪ a history of failure to take medication ▪ degenerative disease involving motor or cognitive functioning ▪ any previous adverse or allergic reaction to risperidone. 	Timing of assessment Measures were taken at these intervals over the 22 weeks of the trial: <ul style="list-style-type: none"> ▪ caregiver ratings weekly ▪ clinician ratings bi-weekly. Retention Of 20 recruited, one patient did not complete the high-dose phase and one did not complete the low-dose phase (90% retention). Fifteen completed the second placebo phase.		Authors' conclusions There was clearly a drug effect based on comparing ratings from placebo and risperidone, however, the optimal dose varied from individual to individual and may have been affected by the order in which participants received the doses.	<ul style="list-style-type: none"> ▪ statistical details on results were sparse ▪ reductions in aberrant behaviour may have been confounded with effects of sedation. However, authors argue that other measures of improvement (e.g., compliance) suggest sedation was not debilitating ▪ the improved response in the second phase of treatment, regardless of whether high or low-dose, may be due to gradual improvement over time on treatment.

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McDougle et al. (1998) USA	Evidence level: II Study design RCT Intervention Risperidone Comparison Placebo (lactose) Study setting Outpatients and inpatients of the Clinical Neuroscience Research Unit at the Connecticut Mental Health Centre. Referred from broad range of sources.	Participants N=30/31 (97%) adults with autism or PDD NOS completed at least four weeks of the study (reported on in results using intention-to-treat method). Sample characteristics Sex: 73% male Age (mean \pm SD): 28.1 \pm 7.3 years Age range: 18-43 years Ethnicity: 24 whites, 6 African-Americans, 1 Hispanic. Diagnosis: 55% with autism and 45% with PDD NOS Non/minimally verbal: 52% IQ (mean \pm SD) using the WAIS-R (for verbal patients) and the LIPS (for non-verbal patients): 54.6 \pm 23.9 Previous use of psychotropic drugs: 77% Outpatients: 77% Inclusion criteria <ul style="list-style-type: none"> diagnosed as having autistic disorder or PDD NOS based on consensus agreement of 2 board-certified psychiatrists applying criteria from DSM-IV, Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule. 	Patients were randomised (according to a computer generated list) to 12 weeks of treatment by risperidone or placebo. (Note: an open-label trial followed which is not reported on here). Dosage and route of transmission Patients were drug-free for at least four weeks before the start of the trial. Dosage of risperidone was started at 1 mg (orally) every night and increased by 1 mg daily every three or four days as required to a maximum dose of 10 mg/day as tolerated (i.e., maximum dose achieved after 5 weeks). Daily dose (mean \pm SD): 2.9 \pm 1.3 mg.	Outcome measures Clinician ratings were obtained including the following: <ol style="list-style-type: none"> CGI (rating overall global improvement) modified Y-BOCS (to rate repetitive behaviour, but not repetitive thoughts) SIB-Q (to rate aggression) Ritvo-Freeman Real-Life Rating Scale (overall behavioural symptoms of autism, as well as subscales including sensorimotor behaviours, social relationships, affectual reactions, sensory responses, and language) ten visual analogue scales (VAS) on 10 mood states. 	Effectiveness Of 14 patients receiving risperidone, 8 (57%) "responded" (according to CGI) c.f. none of 16 receiving placebo ($\chi^2=9.72$, $p<0.002$). Patients receiving risperidone c.f. those receiving placebo had the following (as evaluated by the drug X time interaction): <ul style="list-style-type: none"> decreased repetitive behaviour ($F_{3,84}=8.73$, $p<0.001$) decreased aggression ($F_{3,84}=9.22$, $p<0.001$) decreased anxiety or nervousness ($F_{3,84}=4.14$, $p<0.02$) decreased depression ($F_{3,84}=3.38$, $p<0.03$) decreased irritability ($F_{3,84}=4.33$, $p<0.01$) improved overall behavioural symptoms of autism ($F_{3,84}=4.19$, $p<0.02$), including improvements in these subscales: sensorimotor behaviour ($F_{3,84}=4.16$, $p<0.004$), affectual reactions ($F_{3,84}=8.78$, $p<0.001$). 	Comments <ul style="list-style-type: none"> sample fully randomised clinician blinded patient blinded no baseline differences suggesting similar samples in each condition well validated diagnostic and rating tests. No mention of whether a validated scale was used to record adverse events follow-up was reasonable at 12 weeks relatively small sample reducing statistical power, especially to identify adverse events minimal detail of comorbidities present no detail on commencement or duration of side effects but sedation was described as generally mild and transient no adjustment to p value for multiple tests (i.e., some effects may be by chance).

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McDougle et al. (1998) USA (Continued)		<ul style="list-style-type: none"> had at least moderate severity according to CGI, score >10 "compulsion" subscale on Y-BOCS, score >25 on SIB-Q, >0.20 on Ritvo-Freeman Real-Life Rating Scale) parent or legal guardian provided written informed consent (or assent where patients had cognitive limitations). <p>Exclusion criteria</p> <ul style="list-style-type: none"> patients meeting DSM-III-R criteria for schizophrenia or had psychotic symptoms patients with a significant acute medical condition women with positive serum pregnancy results. <p>Additional screening included: medical history, full physical and neurologic examinations.</p> <p>No statistical differences were evident between intervention and control groups at baseline in age, sex distribution, diagnostic subtype, IQ, treatment setting, or intervention dose.</p>	<p>Chloral hydrate given up to 2 g/day as required to manage agitation.</p> <p>Blinding The capsules used were identical in appearance. Patients, clinicians administering drug and clinicians rating outcomes were all blinded to treatment used.</p> <p>Timing of assessment measures were taken at:</p> <ul style="list-style-type: none"> baseline (two assessments in separate clinic visits) after 4 weeks of treatment after 8 weeks of treatment after 12 weeks of treatment. <p>Retention Of 31 recruited, 7 dropped out. Reasons for dropping out of the study included: agitation (5 patients, with one on active drug), abnormal gait (one patient on active drug), lack of improvement (one on active drug).</p>	<p>Adverse events At each assessment point the following were measured: standing and sitting blood pressure, pulse rate, temperature, respiratory rate, weight. Patients were also systematically examined for extrapyramidal and other adverse events at each assessment.</p> <p>Statistics Of seven patients who dropped out of the 12 week trial, six completed four weeks and the last-observation-carried-forward, intention-to-treat method was used. Analyses reported here are for the intention-to-treat sample (n=30).</p>	<p>No difference in sensory responses, social behaviour, language outcomes, or the following items on the cVAS: "calm", "eye contact", "happy", "restless", "social interaction", "talkative", "tired".</p> <p>Safety No changes in blood pressure, temperature, heart or respiratory rate, and no evidence of acute extrapyramidal effects, cardiac events, or seizures. One patient was withdrawn at four weeks due to the development of abnormal gait.</p> <p>Thirteen (87%) of 15 patients receiving risperidone had at least one adverse event, including: sedation (n=7), weight gain (n=2), agitation (n=2), dry mouth, dyspepsia, diarrhoea, constipation, enuresis, or sialorrhoea (n=1 for each event). This compares to five (31%) patients receiving placebo observed with agitation.</p> <p>Authors' conclusions Risperidone is more effective than placebo in the short-term treatment of symptoms of autism in adults.</p>	

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Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
McDougle et al. (1996) USA	<p>Evidence level: II</p> <p>Study design RCTs, including cross-over design.</p> <p>Intervention Fluvoxamine</p> <p>Comparison Placebo (lactose)</p> <p>Study setting Inpatients and outpatients of the Clinical Neuroscience Research Unit. Outpatients were seen in the Adult Pervasive Developmental Disorders Clinic.</p>	<p>Participants N=30/30 (100%) adults with autistic disorder completed the study.</p> <p>Sample characteristics Sex: 90% male Age (mean±SD): 30.1 ± 7.7 years Age range: 18-53 years</p> <p>Diagnosis: 100% with autistic disorder Non/minimally verbal: 13% IQ (mean ± SD) using the WAIS-R (for verbal patients) and the LIPS (for non-verbal patients): 79.9 ± 29.7 Outpatients: 70%</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ diagnosed as having autistic disorder based on DSM-III-R and ICD-10 criteria ▪ had at least moderate severity according to CGI scale ▪ parent or legal guardian provided written informed consent (or assent where patients had cognitive limitations) 	<p>Patients were randomised to 12 weeks of treatment by Fluvoxamine or placebo.</p> <p>Dosage and route of transmission Patients were drug-free for at least 6 weeks before the start of the trial. Dosage of fluvoxamine was started at 50 mg (orally) every night and increased by 50 mg daily every 3 or 4 days to a maximum dosage of 300 mg/day as tolerated. Mean daily dose=276.7 mg.</p> <p>Blinding The capsules used were identical in appearance. Patients and clinicians were blinded to treatment used.</p> <p>Timing of assessment Measures were taken at:</p> <ul style="list-style-type: none"> ▪ baseline (first 2 clinic visits) and, ▪ after 4 weeks of treatment ▪ after 8 weeks of treatment ▪ after 12 weeks of treatment. 	<p>Outcome measures</p> <p>Clinician ratings were obtained using the following measures:</p> <ol style="list-style-type: none"> 1. Clinical Global Impression (CGI) Scale 2. Autism Diagnostic Interview 3. Autism Diagnostic Observation Schedule. <p>Full scale IQ was assessed using the Wechsler Adult Intelligence Scale-Revised (for verbal patients) and the Leiter International Performance Scale (for non-verbal patients).</p> <p>Parent/guardian ratings were obtained using the Autism Behavior Checklist.</p> <p>Specific symptoms were assessed using the following measures:</p> <ul style="list-style-type: none"> ▪ modified Y-BOCS (to rate repetitive behaviour). 	<p>Effectiveness Of 15 patients receiving fluvoxamine, 8 (53%) "responded" (according to the CGI) c.f. none of the 15 in the placebo group (p=0.001)</p> <p>Treatment response was not correlated with age, level of autistic behaviour, or full-scale IQ.</p> <p>Patients receiving fluvoxamine c.f. those receiving placebo had the following responses at week 12:</p> <ul style="list-style-type: none"> ▪ reduction in total Y-BOCS scores ($F_{1,27}=13.62$, $p<0.001$) ▪ decreased repetitive thoughts ($F_{1,27}=6.36$, $p<0.02$) ▪ decreased repetitive behaviour ($F_{1,27}=18.19$, $p<0.001$). 	<p>Comments</p> <ul style="list-style-type: none"> ▪ sample fully randomised ▪ clinician blinded ▪ patient blinded ▪ no baseline differences suggesting similar samples in each condition ▪ well validated diagnostic and rating tests, however Y-BOCS was "modified" without validation ▪ minimal detail of diagnostic groups represented ▪ no adjustment to p value for multiple tests (i.e., some effects may be by chance) ▪ ethnicity of patients and previous use of psychotropic drugs not reported ▪ follow-up was relatively short at 12 weeks.

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McDougle et al. (1996) USA (Continued)		<p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ if patients met DSM-III-R criteria for schizophrenia or had psychotic symptoms ▪ if patients had abused illicit substances within the previous 6 months ▪ if a notable medical condition, including seizure disorder, was identified ▪ women with positive serum pregnancy results. <p>Additional screening included: medical history, full physical and neurologic examinations. Pulse rate, sitting and standing blood pressure were measured. Patients were also examined for electrocardiographic changes and other adverse events, including anticholinergic side effects, seizures and dyskinesias.</p> <p>No statistical differences found between intervention and control groups at baseline in age, sex distribution, full-scale IQ, ABC scores or intervention dose.</p>		<ul style="list-style-type: none"> ▪ modified Brown Aggression Scale, a 9-category instrument (to rate aggressive behaviour) ▪ Ritvo-Freeman Real-Life Rating Scale (various subscales) ▪ Vineland Adaptive Behavior Scale maladaptive behaviour subscales (parts 1 and 2). <p>Safety No anticholinergic adverse effects developed and no significant changes in pulse or sitting or standing blood pressure occurred. No laboratory or ECG changes could be attributed to fluvoxamine, and no seizures or dyskinesias were observed.</p> <p>Adverse events There were no medically significant adverse events reported in the fluvoxamine group. Minor side effects including nausea and moderate sedation were reported in the treatment and placebo groups.</p>	<ul style="list-style-type: none"> ▪ reduction in maladaptive behaviours ($F_{1,27}=19.47$, $p<0.001$) ▪ decrease in aggressive symptoms ($F_{1,27}=6.40$, $p<0.02$) ▪ improved overall behavioural symptoms of autism ($F_{1,27}=5.02$, $p<0.03$), the drug X time interactions for subscales were not significantly different except for language usage ($F_{1,27}=10.95$, $p<0.003$). <p>Authors' conclusions Fluvoxamine is more effective than placebo in the short-term treatment of the symptoms of autistic disorder in adults.</p>	

Table 5. Primary research studies appraised relating to the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
Willemssen-Swinkels et al (1995) The Netherlands	Evidence level: II Study design Three RCTs, including two with cross-over designs. Intervention Naltrexone hydrochloride, an opioid antagonist Comparison Placebo Study setting Residents of a public institution for mentally retarded persons.	Participants N=32/33 (97%) adults with mental retardation completed the trial. Sample characteristics Sex: 82% male Age (mean ± SD): 29 ± 6 years Age range: 18-46 years Diagnosis: 73% with autism (71% expressed SIB), 27% with daily, moderate to high levels of SIB. Five had history of epilepsy and were being treated with antiepileptics. Nine (27%) had other comorbidities: congenital anomalies of unknown origin (n=6), Down's syndrome (n=1), congenital hydrocephalus (n=1), Hunter's syndrome (n=1). Mental retardation: ranged from mild to profound. Current use of neuroleptics: 33% (concomitant medications remained fixed throughout study).	Patients first received a placebo once a day (patient-blinded only) for two weeks (compliance phase). At week 3, participants were randomised to receive a single mid-range dose of naltrexone hydrochloride, or placebo, followed by placebo for the rest of the week (single dose trial). At week 4, patients were randomised to receive a treatment sequence of either naltrexone followed by placebo, or vice-versa ("long-term" treatment phase). This was followed by a 4-week period without treatment (washout phase). Finally there was a 4-week cross-over to the other treatment (cross-over phase).	Outcome Measures Ratings were made by both staff on the ward, and by workshop staff members during their daily programme, for the following: 1. Aberrant Behaviour Checklist (ABC), including factors of irritability, social withdrawal/lethargy, stereotypy, hyperactivity, excessive speech, and items on SIB-Q, 2. Checklist of target behaviours, including SIB and stereotypic and compulsive behaviours, specific for each patient (e.g., "face-hitting", "self-scratching"), which were rated using a 5-point scale. In addition, staff rated (by consensus agreement) participants' overall global behavioural improvement using the CGI.	Effectiveness Single dose trial: There were no significant drug effects either on total or subscale scores of the questionnaire measures or observational data (data not reported). There were no interactions between whether participants received the single dose of naltrexone or not and their behavioural or liver function response in the following four week intervention trials. Four week treatment trial There were no significant drug effects related to the questionnaire measures or observational data (data not reported) for either dose of naltrexone used, except on the ABC stereotypy subscale as rated by ward staff where stereotypy increased after four weeks of naltrexone treatment; $F(1,27)=6.33$; $p=0.018$. The increase was independent of diagnosis (SIB or autism) or dose.	Comments <ul style="list-style-type: none">▪ sample fully randomised▪ clinician blinded▪ patient blinded▪ sample initially to only include people with autism, but was expanded during the study to include people with at least moderate SIB. Diagnosis was considered as a factor in analyses▪ relatively small sample, reducing ability to identify adverse events, although cross-over design increases validity and generalisability of conclusions.

Table 5. Primary research studies appraised relating to the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
Willemssen-Swinkels et al (1995) The Netherlands (Continued)		<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ diagnosed as having autistic disorder based on consensus agreement of two clinicians applying criteria from DSM-III-R (though not covered by the criteria, study also included nine people with moderate to high levels of SIB on a daily basis for a "long time") ▪ legal guardian and management staff provided informed consent. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▪ none described. 	<p>Dosage and route of transmission Naltrexone hydrochloride was given by oral capsule.</p> <p>During the single dose phase, patients received a mid-range dose of 100 mg (mean±SD=1.61 ± 0.24 mg/kg) of the treatment.</p> <p>During the treatment and cross-over phases, 19 people received low-dose naltrexone (50 mg/day; mean=0.80 ± 0.13 mg/kg) and 14 received high-dose naltrexone (150 mg/day, mean=2.45 ± 0.33 mg/kg). The change was in response to a lack of effect in treatment.</p> <p>The low-dose trial group consisted of two patients with autism, 11 with autism and SIB, and six with SIB only). The high-dose trial group consisted of five with autism, six with autism and SIB, and three with SIB only.</p>	<p>Only 11 patients from the low-dose cohort received direct observations. Two separate ten-minute observations were made at each assessment during a study participant's free time with other residents and ward staff present. The observer was a trained ethology student recording 15 behavioural elements using "The Observer" software. Interrater reliability was reported as being 70% for social behaviour and more than 90% for SIB, stereotypy, and activity behaviours.</p> <p>Adverse events At each assessment point, adverse effects were assessed by the research team "systematically" through "active questioning" of the staff and participants. Liver function was screened to assess safety. Plasma β-endorphin and plasma cortisol levels were assessed by venipunctures and radioimmunoassays two weeks prior to and the day after the single dose of naltrexone hydrochloride.</p>	<p>The lack of therapeutic effect was independent of the age or sex of participants, level of retardation, sensitivity to pain, or whether they were receiving neuroleptic, or any other, concomitant medication.</p> <p>Staff CGI ratings of patients (ranging from much worse to much better) after four weeks of treatment with naltrexone (50 mg) or placebo revealed that placebo was preferred to naltrexone for 12 patients, and naltrexone preferred to placebo for only four patients. The placebo treatment was significantly more successful than the naltrexone treatment (paired t test, 2.36; df=18, p=0.03). For the higher 150 mg dose, naltrexone's success equalled that of the placebo.</p>	<ul style="list-style-type: none"> ▪ patients initially received a lower dose of the drug but this was increased mid-trial as the low-dose was found to be ineffective. This means that there were essentially two cross-over trials conducted, with a high-dose (n=19) and low-dose (n=11) intervention. Patient characteristics for each cohort were not presented except for diagnosis, and were not statistically compared at baseline. It is possible that patients who entered the trial earlier may have been systematically different, or been treated or observed differently, from those who entered later as the trial progressed ▪ patients were administered fixed doses of naltrexone instead of titrating on an individual basis, which may have led to increased effectiveness.

Table 5. Primary research studies appraised relating to the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
Willemssen-Swinkels et al (1995) The Netherlands (Continued)			<p>Blinding Patients, clinicians administering drug and clinicians rating outcomes were all blinded to treatment used.</p> <p>Timing of rating assessments Direct observation: Assessments were taken at the following intervals: twice at baseline, six and 24 hours after the single-dose administration, and after two and four weeks of daily treatment during both treatment and cross-over phases.</p>	<p>Statistics Repeated measures ANOVA were used to investigate the effect of the single dose of naltrexone hydrochloride with drug condition as a within-subject factor and diagnosis as a between-subject factor.</p> <p>A similar ANOVA was used to investigate the effect of four weeks of naltrexone hydrochloride with an additional within-subject factor of time (two weeks and four weeks of treatment/placebo), and the additional between-subject factor of dose (50 mg or 150 mg). Baseline outcome scores were used as covariates. Two-tailed significance tests were used with alpha=0.05.</p>	<p>Safety One woman receiving daily 50 mg doses of naltrexone hydrochloride demonstrated a severe increase in SIB and "acting-out" behaviour, requiring isolation for several weeks, subsequent discontinuation from the trial and exclusion from the analysed dataset. Another woman receiving the same dose reported nausea and tiredness.</p> <p>Three participants exhibited sedation whilst receiving daily 150 mg doses of naltrexone.</p> <p>Liver function tests were normal for all trial participants.</p>	<ul style="list-style-type: none"> ▪ Outcome measures included well-validated tests as well as a checklist of target behaviours which was developed for the study. No psychometric data describing the checklist's reliability or validity was presented. Direct observations were only made on 11 participants from the first cohort of n=19 receiving low-dose treatment, and not all 32 for "practical reasons". This may suggest bias in the sample selected for direct observation.

Table 5. Primary research studies appraised relating to the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder (continued)

Authors, country	Evidence level, study design, comparisons, study setting	Sample characteristics, inclusion and exclusion criteria	Methods	Outcome measures	Results, authors' conclusions	Comments on strengths and limitations
<p>Willemsen-Swinkels et al (1995)</p> <p>The Netherlands</p> <p>(Continued)</p>			<p>Other measures were taken at:</p> <ul style="list-style-type: none"> ▪ baseline (at beginning and end of 2 week compliance placebo phase) ▪ after the single dose phase ▪ after the 4 week low-dose or high-dose treatment/placebo phase. <p>Retention Of 33 recruited, one woman was withdrawn due to increase in SIB (see results column under "adverse events").</p>		<p>In the single-dose study, plasma cortisol levels were significantly increased from placebo (mean=300nmol/L) after Naltrexone treatment (mean=360 nmol/L; (F(1,29)=8.84; p=0.006).</p> <p>Authors' conclusions Naltrexone failed to have therapeutic effects on SIB or autism. Naltrexone hydrochloride in a 50 mg/day dose may even aggravate behaviour problems.</p>	<ul style="list-style-type: none"> ▪ no mention of whether a validated scale was used to record adverse events ▪ blood samples for plasma tests were collected the day after drug administration, therefore may have missed short-lasting effects of naltrexone ▪ follow-up was relatively short at 4 weeks ▪ the participant who withdrew due to a severe adverse response could have been included in analyses on an intention-to-treat basis ▪ no adjustment to p value for multiple tests (i.e., some effects may be by chance).

Key:

ASD: Autism Spectrum Disorder

ABC-C: Aberrant Behaviour Checklist – Community

ANOVA: analysis of variance

CGI: Clinical Global Impressions Scale.

DOTES: Dosage Treatment Emergent Symptom Scale

EPS: extrapyramidal side effects

ESRS: Extrapyramidal Symptom Rating Scale

LIPS: Leiter International Performance Scale

mg/day: milligrams per day

mg/d/kg: milligrams per day per kilogram

ns: not significant

PDD NOS: Pervasive Developmental Disorder Not Otherwise Specified

RCT: randomised controlled trial

SIB-Q: Self-Injurious Behaviour Questionnaire

VAS: visual analogue scales

WAIS-R: Wechsler Adult Intelligence Scale-Revised

Y-BOCS: Yale-Brown Obsessive Compulsive Scale

Conclusions relevant to primary studies appraised

The search identified five eligible primary research studies.

Two studies investigated the effectiveness of risperidone. McDougle et al. (1998) considered 31 adults with autism or PDD NOS in a double-blind RCT of 12 weeks duration. The double-blind, randomised controlled cross-over trial of Zarcone et al. (2001) considered 20 people (75% of whom were over 12 years of age), mainly with autism or PDD NOS, who had an extended history of severe self-injurious behaviour, aggression, property destruction or stereotyped movements. The trial, also of 12 weeks, was split between consecutive six weekly high-dose and low-dose phases. Despite differences in sample characteristics, study design and outcome measures, both studies categorised 50 percent of their treatment samples as “responders” as determined by different measures of global improvement. McDougle and colleagues (1998) also reported improvements on repetitive behaviours, aggression, self-injury, motor-hyperactivity and some mood states (depression, irritability and nervousness), though not on social functioning or language outcomes. The trials were too small to reliably estimate risks for adverse events; however, risperidone appears to have been relatively well tolerated. Common side effects, notably sedation and weight gain, were noted but generally were not severe enough to necessitate withdrawal from these trials. As acknowledged by Zarcone et al. (2001), some behavioural effects may be confounded by the drug’s affect on sedation, although this is unlikely to explain all improvements. Overall, there appears to be preliminary evidence that risperidone may be effective in reducing behavioural problems associated with autism in the short-term.

Willemsen-Swinkels et al. (1995) evaluated naltrexone hydrochloride in a sample of 33 adult institutional residents, with autism and/or self-injurious behaviour. In double-blind RCTs, neither a one-off moderate dose or four weeks of low or high-dose naltrexone had positive impact on behavioural features of autism or on self-injurious behaviour. Uncommon adverse events included sedation and nausea. These results suggest that short-term treatment with naltrexone hydrochloride is unlikely to be beneficial in managing autism.

In the only study to evaluate an SSRI, McDougle et al. (McDougle et al. (1996b)) considered 30 adults with autism in a 12 week long double-blind, randomised controlled trial of fluvoxamine. More than half the sample receiving fluvoxamine “responded” in terms of global improvement. Compared with placebo, the treatment group exhibited significant decreases in repetitive thoughts, repetitive behaviours, maladaptive behaviours and aggression, and improvement in language usage and overall behavioural symptoms of autism. However, fluvoxamine did not appear to influence sensorimotor behaviours, sensory responses, social relationship to others and expressions of affect. Relatively minor side effects were reported within both the treatment and placebo groups. The results show promise that fluvoxamine may provide (at least short-term) benefit in reducing some behaviours associated with autism.

A double-blind, randomised controlled trial (Remington et al. 2001) investigated the short-term effectiveness of two interventions, clomipramine and haloperidol, in 37 patients with autism aged 10 to 36 years (mean age=16.3 years). Patients received up to seven weeks treatment of each of clomipramine, placebo, and haloperidol in a trial, and participated in three separate trials to allow the order of each treatment phase to be varied systematically. Results across the three trials using an intention-to-treat analysis suggest that for the patients receiving haloperidol compared with placebo, there were reductions in the overall severity of symptoms of autism as well as specific reductions in irritability and hyperactivity. Similar reductions were not reported for patients receiving clomipramine. There was no change in stereotypic behaviour, lethargy or inappropriate speech observed for either treatment group. A re-analysis of participants who completed trials suggested similar improvement compared to baseline in the clomipramine and haloperidol phases respectively. However, as significantly fewer individuals treated with clomipramine were able to complete treatment, this secondary analysis of a biased and reduced sample should be interpreted with caution. There were no significant adverse events and no significant differences in extrapyramidal symptoms between treatment groups. Relatively minor side effects were reported during treatment, the most common being fatigue and lethargy.

Methodological limitations of this research base and recommendations for future research are discussed in the next chapter.

Chapter 4: Discussion

4.1 SUMMARY OF EVIDENCE

Search strategy, article selection and appraisal methods

This report reviewed the international evidence relating to the effectiveness of drug therapies for young people and adults with Autism Spectrum Disorder. A systematic method of literature searching, selection and appraisal was employed in the preparation of this report.

An extensive search strategy included eight bibliographic databases, five electronic and library catalogue sources, major online library catalogues, and relevant government and health professional website sources. Relevant publications referenced in retrieved material were also identified.

Primary research studies were included if they reported on samples of at least 10 adolescents or adults (with a mean/median age of at least 13 years), primarily with ASD. Inclusion criteria also specified that studies evaluated pharmacological interventions which were currently available internationally compared with a placebo/comparison treatment. Effectiveness (measured using at least one quantitative/standardised measure) needed to be evaluated relevant to improvement to core and/or associated features of ASD or quality of life for the person with ASD or their family/carers. Studies were excluded if they primarily concerned participants with dementia, were case series reports, or were narrative (non-systematic) reviews, correspondence, book chapters, or articles published in abstract form. Systematic reviews were considered which had study selection criteria that at least overlapped with those of the current review and therefore had the possibility of including papers eligible for this review, even if no such papers were identified.

The authors (Ms Broadstock and Dr Doughty) independently applied predetermined selection criteria to identify primary studies for appraisal. There was 100 percent concordance in selection. Each primary study was classified according to National Health and Medical Research Council (NHMRC 2000) levels of evidence criteria.

Approximately 1,500 articles were identified by the search strategy. From 50 articles identified as potentially eligible for inclusion, a final group of 12 papers was selected for appraisal, including five primary research studies and seven systematic reviews. More than half of the exclusions were because the studies focused on children. The main results are presented below.

Secondary studies

Seven systematic reviews were identified which potentially may have included articles eligible for appraisal in the current review.

Two reviews considered atypical anti-psychotics. Barnard et al. (2002), looking at the use of these drugs in managing autistic disorder, conducted a relatively limited search. Nineteen studies were identified for appraisal, including two double-blind cross-over, randomised controlled trials. The authors reported that risperidone may be effective in reducing hyperactivity, aggression, and repetitive behaviours. They also noted the possibility that olanzapine and quetiapine may be effective. There was little evidence for the effectiveness of amisulpride or quetiapine in managing ASD. Barnard et al. (2002) called for randomised trials in the use of atypical antipsychotics in patients with autism. Toren et al. (1998) conducted an earlier review also looking at the use of atypical anti-psychotics in children and adolescents (but without a focus on autism). Their search of a single database identified 62 studies, including five placebo-controlled clinical trials. Small samples, short duration of treatments, and the lack of double-blind controlled trials in the field all limited the authors' ability to make conclusions about effectiveness. They called for systematic research into dose-response and dose-risk relationships.

There was one review on the use of antiepileptic (anticonvulsant) drugs in the treatment of autism (Di Martino and Tuchman 2001). A very limited search strategy identified 10 studies for appraisal; none of which were controlled trials. The studies primarily concerned children, more than half of whom had comorbid epilepsy. Whilst some improvements were reported in a variety of domains for several medications, all of the studies were small, uncontrolled and methodologically difficult to compare. The authors call for randomised trials on the application of anticonvulsants for treatment of people with both autism and epilepsy.

A very limited search of the literature examining the effectiveness of secretin in the management of autism was conducted by Patel et al. (2002). Eight RCTs were appraised. Most of the double-blind placebo-controlled studies reviewed did not report any improvements in behaviour across a number of measures. Methodological limitations included the lack of an intention-to-treat approach to analyses which may have introduced a positive response bias in many of the studies. The authors suggest that future double-blind, placebo-controlled studies of secretin should adopt standardised methods and assessment procedures to enable meaningful conclusions to be drawn. A Cochrane systematic review of intravenous secretin which excluded adults and people with comorbidities is currently in the protocol stage (Williams et al. 2003).

Finally, three systematic reviews dealt with vitamin therapy. The most comprehensive and methodologically sound of these was recently conducted for the Cochrane Collaboration by Nye and Brice (Nye and Brice 2002). It considered the efficacy of vitamin B6 (pyridoxine) and magnesium for treating social, communication and behavioural responses of people with autism. Only fully randomised placebo controlled trials were appraised, and two studies were identified for appraisal. The authors concluded that there is no reliable evidence that combined vitamin B6 and magnesium improve the behaviour of children with autism. They suggested that future research include multi-centre trials with larger sample sizes, longer periods of treatment, and the use of a broader range of outcome measures.

Compared to the review above, a moderately broad but less restrictive search on the same topic by Pfeiffer et al. (1995) also included a review of the methodology of studies in the area. A dozen studies were appraised, most from the same two treatment centres, including seven RCTs. Most studies reported moderate to marked behavioural improvements following treatment with vitamin B6 and magnesium, however these positive findings should be interpreted cautiously in the light of methodological limitations that include imprecise outcome measures, small samples, and short-term follow-up.

Another moderately broad search of the literature published up to the 1990's considered the effects of niacin, vitamin B6, and other multivitamins on mental functioning, but did not restrict itself to studies of people with autism (Kleijnen and Knipschild 1991). Of 53 trials identified, five were cross-over trials involving children with autism treated with very high doses of vitamin B6 alone or combined with magnesium. Whilst there were some positive findings in relation to effectiveness, these studies were generally flawed by the use of small samples, and lack of detail reported on baseline characteristics, changes in concomitant treatment, and presentation of statistics, and therefore no conclusions could be drawn.

Across all of the seven systematic reviews appraised, authors agreed about the need for more double-blind randomised controlled trials. They also consistently stated that these trials should focus on recruiting larger samples and implementing longer treatment and follow-up phases. Standardised outcome measures, more detailed reporting of baseline characteristics and clear presentation of results, including statistical tests, would increase the likelihood of relevant and appropriate conclusions.

Primary studies

The search identified five eligible primary research studies. All included placebo control arms, some randomisation in participant allocation, and double-blinding, although compromises in these strategies were evident in some papers. All five studies were graded as Level II evidence according to the NHMRC hierarchy of evidence (see **Appendix 2**), which reflects high-level evidence. The pharmacotherapeutic interventions evaluated in these studies included risperidone in two trials (McDougle et al. 1998; Zarcone et al. 2001); the opioid antagonist, naltrexone hydrochloride

(Willemsen-Swinkels et al. 1995); fluvoxamine (McDougle et al. 1996b); and a comparison of clomipramine and haloperidol (Remington et al. 2001). Dosages in four of the studies were initially prescribed and then titrated upwards, as tolerated, with the exception of Willemsen-Swinkels et al.'s study (1995) which employed set dose regimens.

Three of the studies were conducted in the USA, one in Canada, and one in The Netherlands. Samples sizes were all relatively small, ranging from 20 to 37 participants (mean = 30.2) and where studies were not cross-over trials, the intervention arm sample size was further reduced. Participants included those from hospital or research clinic inpatient or outpatient settings, or a combination of both. Three studies concerned adults alone and two studies considered children, adolescents and adults (whilst meeting the selection criteria for this review in regard to mean age). In four of the primary studies appraised, the populations were predominantly male (ranging from 73% to 90%), which probably reflects the gender bias in incidence of autism where four times as many males are affected as females (Smalley et al. 1988). In one study (Zarcone et al. 2001), half of the sample was female.

The samples for each of the included studies were either predominantly or totally people with ASD. Self-injurious behaviour (SIB) and aggression were also present in a large proportion of the sample in two studies. Information on participants' physical or psychiatric comorbidities was rare, and only reported in one study (Zarcone et al. 2001). Standardised scales for measuring clinician/staff ratings of global behavioural improvement, and ratings by clinical staff or carers of specific behavioural dimensions such as aggression and repetitive behaviour, were present in all studies. Mood states and other specific symptoms of autism and were sometimes measured.

Across the five studies, individual trials were too small to reliably estimate the risk of adverse events, however all studies provided at least some information about safety outcomes. The methods for measuring adverse events were quite diverse, ranging from a very informal approach to the use of systematic questioning, and (in one study) the use of published rating scales. Physical and/or physiological outcomes were measured in many studies, where relevant to the safety profile of the treatment – e.g., weight change, blood pressure, pulse and temperature measurements, ECG/cardiac monitoring, liver functioning and plasma indices.

McDougle et al. (1998) and Zarcone et al. (2001) investigated the effectiveness of the atypical antipsychotic risperidone in separate 12 week trials. Despite differences in sample characteristics, study design and outcome measures, both studies categorised half their participants receiving treatment as “responders”, as determined by different measures of global improvement. McDougle and colleagues (1998) also reported improvements in repetitive behaviours, aggression, self-injury, motor-hyperactivity and some mood states (depression, irritability and nervousness), though not on social functioning or language outcomes. Risperidone was well tolerated. Whilst sedation and weight gain were common side effects, generally the side effects experienced were usually not severe enough to lead to withdrawal from these trials. Overall, there appears to be preliminary evidence that risperidone may be effective in reducing behavioural problems associated with autism in the short-term. Further research with larger samples would be desirable.

In their investigation of naltrexone hydrochloride, Willemsen-Swinkels et al. (1995) concluded that neither a one-off moderate dose, or four weeks of low or high-dose naltrexone, had a positive impact on behavioural features of autism or on self-injurious behaviour. Uncommon adverse events included sedation, nausea and an isolated case of increased self-injurious behaviour. These results suggest that short-term treatment with naltrexone hydrochloride is unlikely to be beneficial for managing autism.

Only one study was appraised that looked at an SSRI antidepressant. McDougle et al. (1996b) reported that more than half of the sample receiving the SSRI fluvoxamine “responded” in terms of global improvement after 12 weeks of treatment. Compared with placebo, there were significant decreases within the treatment group in repetitive thoughts and behaviours, maladaptive behaviours and aggression, and significant improvement in language usage and in the overall behavioural symptoms of autism. However, fluvoxamine did not influence sensorimotor behaviours, sensory responses, social relationships to others, and expressions of affect. Relatively minor side effects were reported in both the treatment and placebo groups. The results of this small study show promise that fluvoxamine may be of (at least short-term) benefit in reducing some behaviours associated with autism.

In the only study to compare drugs from different classes, Remington et al. (2001) investigated the short-term effectiveness of two interventions, clomipramine and haloperidol, compared with placebo, in treatment phases of up to seven weeks across three trials with varied phase order. Results across the three trials suggest that for the patients receiving haloperidol compared with placebo, there were reductions in the overall severity of symptoms of autism as well as specific reductions in irritability and hyperactivity. Similar reductions were not observed in patients receiving clomipramine in intention-to-treat analyses. There were no changes in stereotypic behaviour, lethargy or inappropriate speech with either intervention. Differences in the proportion of individuals who completed treatment phases for each trial meant that statistical comparisons between treatments were difficult to interpret.

4.2 LIMITATIONS OF CURRENT RESEARCH BASE

The evidence considered in this review exhibited methodological limitations, which are summarised below.

Study design

Few studies were identified which met our quality criteria, suggesting that there is a dearth of high quality research in this area. This is particularly the case with respect to study design, with most research in the field being uncontrolled case series, including single-subject reports. Whilst these have been useful in the development of new strategies and individualising treatment, they do not control for maturation (especially with respect of developmental phenomena), placebo effects, or experimenter artifacts (Lord 2000). Fully randomised placebo-controlled trials are exceptionally rare and only five were identified which met the selection criteria for this review (although more would have been identified if the scope was extended to studies of children with autism).

Among the studies we considered in this review, there were compromises to design quality. The most significant problem was small sample size with on average a total sample of approximately 30 patients. This number was often further reduced by allocation to placebo or treatment conditions in studies which were not cross-over trials, and participant attrition due to side effects. There are many limitations that may result from trials of restricted sample size. Having a small pool of participants can compromise the benefits of random assignment in balancing the treatment and placebo groups with respect to baseline characteristics. This can be problematic where potentially confounding characteristics (such as severity of illness, comorbidities, age) interact with response to treatment. A common, associated flaw can be the lack of any systematic comparison between treatment groups at baseline to see whether randomisation was successful in producing similar comparison groups prior to treatment. Cross-over trials can be efficient for small samples in providing equivalent placebo and treatment groups; however, they are open to other biases and provide less reliable information than standard RCTs. Regardless of which design is used, small samples reduce the heterogeneity of the sample and therefore the generalisability of results to people with different clinical symptomatology.

A more significant limitation of small-sampled studies, which plagues research in autism, is that they are under-powered and therefore unable to provide precise estimates of effectiveness. This issue is more pronounced with respect to the inability of studies with small samples to detect rarer significant adverse events or to allow meaningful estimates of risk for side effects. None of the studies appraised computed relative risk ratios and the small samples generally precluded multivariate analyses, which can systematically investigate the effects of multiple confounding or mediating variables. Studies also do not report indicators of precision such as confidence intervals; small samples are likely to lead to wider confidence intervals and estimates that lack precision. Subject withdrawal due to side effects or a lack of a treatment response can reduce sample size, however an intention-to-treat approach permits analysis of the enrolled sample and ensures that such patient attrition does not bias the trial results. However, it is also possible that where samples are very heterogenous, subgroups may respond to a drug differently. Including participants who have withdrawn due to lack of effect may disguise a true effect for a subgroup. Larger samples permitting multifactorial analyses are the best way of managing heterogenous samples. Accepting these points, it is acknowledged that due to the relatively rare prevalence of ASD in the community, sample recruitment is a major challenge to researchers in this area. Strategies to increase sample sizes are possible as discussed in **Section 4.3**.

Whilst double-blindness was often attempted in studies appraised, blindness to treatment condition by staff administering the treatments, as well as staff measuring outcomes, was not always complete. For example, in one trial (Zarcone et al. 2001) there was assessor knowledge of the order of placebo and treatment phases, although assessors were blinded to the length of each phase. Emerging side effects may also alert the patient, or the clinician/carer making outcome assessments, to whether an active drug is being taken. The latter can partially be masked by using different staff to make effectiveness ratings than those who systematically look for adverse events (Scahill et al. 2001).

A design limitation in all the studies considered was their relatively short follow-up period for assessing outcomes post-commencement of treatment. Treatment periods were no longer than 12 weeks, which included the titration period to the optimal dose. In some studies (McDougle et al. 1998; Zarcone et al. 2001), follow-up continued during “maintenance” phases of open-label treatment to enhance the clinical relevance of the trials (Scahill et al. 2001). However, these lacked the controlled, double-blind conditions necessary to make more definitive conclusions about the efficacy of the intervention, particularly given that placebo effects can be strong, as demonstrated in Zarcone et al.’s study (2001).

Sample characteristics

The lack of studies eligible for appraisal was in part due to design quality, and also due to the exclusion of studies relating to children, with more than half of retrieved papers excluded for this reason. There were only three studies appraised relating primarily to adults. The two studies which combined samples of children, adolescents and adults met selection criteria, with their sample mean or median being above 12 years; however, results were not reported separately for the different age groups and a significant minority of participants were children. It is clear that there is scant research available to guide clinicians about the effectiveness or safety of pharmacotherapy for their adolescent or adult patients. As discussed in **Chapter 1**, the variable expression of ASD over the lifespan is likely to lead to different symptoms and support requirements needing management, and to distinct responses to pharmacotherapy treatment in older patients compared to children. For this reason, pubertal status may be considered as a potential confounder that ideally should be equivalent between treatment and placebo groups at baseline (Scahill et al. 2001).

As mentioned above, small sample sizes in this area have led to a narrow range of behavioural and cognitive profiles represented in the patients investigated. ASD is heterogenous in terms of its symptoms as well as its underlying biological causes. Therefore, it is difficult to know which individuals will respond to a treatment because the disease’s manifestation varies greatly between individuals across the spectrum. The efficacy of a drug therapy may also vary depending on when, in relation to the onset of symptoms, a drug is administered. For these reasons, it is very important to have samples that represent a wide range of people with autism with respect to diagnosis, symptomatology, and age.

Restricted recruitment sources may introduce biases into the make-up of samples in this research. Convenience samples from research inpatient clinics were common in the appraised literature, although some studies did make attempts to draw samples from multiple sources, including outpatients referred by case managers, family members and teachers (Zarcone et al. 2001). Randomised controlled trial samples may be more likely to include patients who are more severely affected and who are receiving active treatment (Barnard et al. 2002). People at the “higher functioning” end of the autistic spectrum may not be diagnosed with the disorder, or be diagnosed in adulthood. Indeed, there will be many adults aged over 20 years who do not receive diagnosis or support for ASD (Trevathan et al. 1998). Such participants would be excluded from research studies, which would in turn reduce the generalisability of study findings to these populations. Whilst heterogeneity is important for generalisability, larger sample sizes would be needed to investigate differences in treatment response between different diagnostic groups within the autistic spectrum.

- Whilst generally studies did not exclude participants because of physical and psychiatric comorbidities, there was minimal information provided on these in the appraised studies, with the exception of Zarcone et al. (2001). It could be assumed that the presence of common comorbidities for autism, such as epilepsy and mood disorders, was rarely assessed, however this remains unclear. It is acknowledged that diagnosis of comorbidity in patients who have

communication deficits may be particularly fraught for certain diagnostic groups, such as mood disorder. The absence of this information ignores the possibility that any diagnoses additional to ASD (and drugs prescribed for the comorbidities) may confound response to treatment, and variations in confounding factors at baseline between comparison groups may lead to bias and misleading results.

Treatments/dose

Despite the considerable growth in basic studies and increasing knowledge of core biological and cognitive deficits in autism, there has been relatively little research on new interventions (Tager-Flusberg et al. 2001). The five trials appraised in this review considered only five pharmacotherapy treatments: the atypical antipsychotic risperidone (in two studies); the opioid antagonist naltrexone hydrochloride; the SSRI fluvoxamine; and a comparison of the antidepressant clomipramine with the typical antipsychotic haloperidol.

In addition to the limited range of interventions considered, there was a lack of studies comparing different drugs within the same sample, with one notable exception (Remington et al. 2001). Such information on equivalent samples would facilitate consideration of the respective benefits of these interventions as well as their safety, particularly given the great variation in the expression of autism. Ethical considerations need to be considered in randomised controlled trials in the selection of therapeutic treatment arms. Whilst in some studies there was some information on whether individuals were receiving other therapies (e.g., behavioural, educational), differences in these factors were not systematically investigated within studies (small sample size again contributing to this omission). Unfortunately, there were also no studies involving polypharmacy. These are important limitations in a field where multiple therapies, and multiple drug therapies in particular, are common.

Generally dosages were titrated upwards, as tolerated, from a set base, although Willemsen-Swinkels et al. (1995) employed set dose regimens. Only one study systematically investigated dose-effect, and found none (Zarcone et al. 2001). A possible reason is that optimal doses are best determined for each patient in relation to their symptom profile, degree of drug tolerance, and side effects experienced. Adherence to dose regimen is frequently a problem in this field. The completion of diaries recording daily drug intake by the patient or carers may assist and is preferable to the taking of regular blood samples, which are invasive and difficult practically in this population (Scahill et al. 2001).

With respect to generalisability to New Zealand, generally SSRIs and risperidone are the most commonly used drug therapies for managing ASD and associated conditions. Medication choice is influenced to a large degree by the specific target symptom or suspected underlying comorbid psychiatric condition. With individuals with complex or particularly severe presentations, polypharmacy is not uncommon. Of those interventions considered in appraised trials, fluvoxamine is not available currently, and naltrexone hydrochloride is available but not subsidised by PHARMAC.

Mean daily doses given to patients in some included studies differed from those routinely used in New Zealand. In the study by McDougale et al. (1998) risperidone was gradually increased to 10 mg/day as individually tolerated. Doses greater than 6 to 9 mg/day would be extremely unusual in New Zealand. Finally, in Remington et al.'s (2001) trial of two pharmacological interventions, a mean daily dose administered for clomipramine of 128 mg would be considered to be relatively low compared with New Zealand where 150 mg is regarded as a reasonable target dose. Haloperidol's mean daily dose (1.3 mg), and the daily dose used for risperidone in Zarcone et al.'s (2001) study were within the range of those generally used in New Zealand.

Outcomes and interpretation

Outcome measures employed in the studies appraised commonly included clinician ratings of global behavioural improvement, and of specific behavioural dimensions such as aggression and repetitive behaviour. Less frequently assessed were mood states and other specific symptoms of autism. Cognitive outcomes were rarely investigated. It has been suggested that a broader range of outcome measures could be fruitfully employed, including quality of life, readiness for education, independence,

and daily living skills (Nye and Brice 2002). Whilst psychometrically tested scales are available for some of these outcomes (such as quality of life), other outcomes may currently lack scales designed specifically for, and standardised with respect of, people with ASD.

Researchers and clinicians need to consider not just the statistical significance of differences in outcomes measures but also the magnitude of the effects and their clinical significance, especially with respect to the person with autism's quality of life and that of their carers. As mentioned earlier, some features of autism are not regarded as problematic by some individuals with autism and may not require treatment, particularly if they do not interfere with their lifestyle, employment or independence.

4.3 DIRECTIONS FOR FUTURE RESEARCH

Future research should attempt to address the methodological limitations in study design identified in the selection and appraisal of primary studies for this review, and in the systematic reviews also appraised within the field. Features of future research are presented briefly below, and are expected to lead to higher quality studies with more informative and reliable evidence.

- Whilst recognising the important role of case-series in preliminary research investigating novel interventions or populations, fully randomised, genuinely double-blind, placebo-controlled trials are required.
- Studies with larger sample sizes (from multi-site collaborations using identical methods and measures) to provide greater statistical power and more precise effect estimates.
- Studies focussing explicitly on adolescent, and adult, populations respectively.
- Use of clear, predetermined methods of sample ascertainment that seek to recruit samples reflecting a broader range of patient characteristics (including diagnosis, symptomatology, and age).
- Detailed reporting of patient characteristics and baseline comparisons of patient characteristics, including diagnoses and physical and psychiatric comorbidities to demonstrate equivalency of treatment and control groups at baseline.
- Detailed reporting of numbers and characteristics of individuals who are excluded from the study, or who withdraw from treatment (Lord 2000).
- Consideration of a broader range of pharmacological interventions, and trials comparing clinically acceptable drugs.
- Studies comparing pharmacological interventions within and between drug classes, including polypharmacy.
- Studies systematically comparing multiple therapies (pharmacological, behavioural, educational) or combinations of these.
- Studies with longer follow-up periods for assessing outcomes post-treatment, particularly safety outcomes, given that autism is a chronic condition and long periods of treatment are to be expected.
- Consistent use of standardised, psychometrically tested diagnostic and assessment tools which allow collaboration across sites necessary to combine results, and increase sample sizes and statistical power. Unfortunately, there is not complete agreement of classifications amongst all of these instruments (Tager-Flusberg et al. 2001).
- Studies with assessment of a broader range of outcomes relating to cognition, quality of life, readiness for education, independence, and daily living skills (Nye and Brice 2002) which have been developed and psychometrically tested for patients with autism and which reflect individual's support needs and preferences.
- Studies with analyses on an intention-to-treat basis to ensure that patients withdrawing due to non-response or side effects do not bias the trial results.
- Studies with more detailed reporting of statistical tests and estimates of precision, including confidence intervals.

- Studies with multivariate analyses to investigate the effects of potentially confounding factors in intervention effectiveness.
- In the field more generally, studies are required into the differences between subtypes of autism across the spectrum of disorder (Tager-Flusberg et al. 2001), and the varying treatment and support needs of these distinct diagnostic groups.
- With respect to multiple pharmacotherapy interventions, drugs that may treat one symptom may exacerbate another, requiring the development of more selective agents (Larkin 1997). Molecular genetic studies receiving extensive research interest may lead to the development of new and effective treatments (Leventhal et al. 1998).

In recognition that pharmacological research in autism is marked by inconsistent findings in small samples that fail to guide clinical practice, the National Institute of Mental Health (NIMH) awarded competitive contracts to establish a five-site network of Research Units on Pediatric Psychopharmacology for autism and PDDs. The RUPP Autism Network's initial study investigated the short-term efficacy and safety of risperidone in children and adolescents with autism in an eight week, double-blind, randomised placebo-controlled trial of 101 patients (Scahill et al. 2002). However, the mean age of the sample was 8.8 years and the study was excluded from the current review when the abstract was considered. The RUPP Autism Network has no plans to conduct studies involving adults at this time although it is agreed that this is an understudied area (Professor Christopher McDougle, *personal communication*, 25 June 2003). Nevertheless, this trial and its design and rationale (McDougle et al. 2000; Posey and McDougle 2001) are instructive in the RUPP Network's attempt to deal with many of the methodological limitations of this field discussed previously.

4.4 CONCLUSIONS

Whilst autism currently cannot be cured, pharmacological interventions have been utilised to assist in managing symptoms and associated conditions of autism, which may be problematic for the person with autism and/or their carers. Such treatments may also enhance the benefit from other concurrent therapies, which include behaviour modification and other psychosocial and educational interventions.

Whilst an extensive literature exists relating to the use of medication in autism, very few studies were identified in this systematic review that related specifically to adolescents or adults, and which were designed to detect evidence of effectiveness and safety. This limits our ability to make specific statements that offer guidance in the management of autism for this population. In the absence of adequately powered, randomised controlled trials with adequate follow-up, only preliminary conclusions can be made.

The conclusions described below are based on our systematic review of the international literature published in English between 1980 and February 2003 on the effectiveness of pharmacological therapies for young people and adults with Autism Spectrum Disorder. Of more than 1,500 studies identified by the extensive search strategy, 50 full text articles were retrieved and after applying selection criteria, 12 papers were deemed eligible for inclusion in the review, including seven systematic reviews and five primary research studies.

Seven systematic reviews were appraised. These considered a range of pharmacological interventions, including atypical antipsychotics, anticonvulsants, secretin and vitamin therapy. Notably, unlike the current systematic review, no review was identified which attempted to look at all pharmacological interventions available for managing ASD. The focus of the seven appraised reviews was predominantly on children, although studies that included adolescents or adults were not excluded. The authors of one of the reviews concluded that there is some evidence that risperidone may be effective in reducing hyperactivity, aggression and repetitive behaviours in those with autism. All of the reviews highlighted the need for more double-blind, randomised controlled trials in this field and emphasised the ways in which recruitment, implementation and reporting of drug trials for ASD could be improved in the future.

Five primary research studies were appraised that met selection criteria for relevance and methodological quality. All five were double-blind, randomised placebo-controlled trials graded as

Level II evidence according to the NHMRC hierarchy of evidence which reflects high-level evidence. However, studies had relatively small sample sizes (mean = 30), and were likely to be statistically underpowered and therefore unlikely to produce precise estimates of effectiveness. Treatment duration evaluated was also relatively brief and no more than 12 weeks. Given these and other limitations, the primary research studies appraised generally provided only preliminary evidence relating to the (at least short-term) effectiveness of medications trialled. Specific evidence is described below.

- Risperidone may be effective in reducing certain behaviours associated with autism, namely aggression, repetitive behaviour and hyperactivity, though not social functioning and language.
- Fluvoxamine may be effective in reducing repetitive thoughts and behaviours, maladaptive behaviours and aggression. Fluvoxamine may also improve language usage, however it does not appear to influence sensorimotor behaviour, sensory response or social relationship to other people. Fluvoxamine is not currently available in New Zealand. It may be a useful addition to the range of medications that are available for people with ASD in this country.
- Haloperidol may be effective in reducing the overall severity of symptoms of autism as well as specifically reducing irritability and hyperactivity. Haloperidol may be more effective than clomipramine in the treatment of autism, although mean daily doses were lower for clomipramine than those routinely used in New Zealand. Neither drug appears to influence stereotypic behaviour, lethargy or inappropriate speech.
- Naltrexone hydrochloride appears to be ineffective in the short-term. Neither a one-off moderate dose, nor four weeks of low or high-dose naltrexone, had a positive impact on behavioural features of autism or specifically on self-injurious behaviour.
- No major adverse events were reported for any of the interventions assessed in the primary studies. However, these small trials were not designed to determine risk estimates and reliable conclusions about these medications' safety profiles cannot be made.
- Generally speaking, no conclusions could be made about the effectiveness of one class of drug over another, or for the treatment of what specific comorbidity.
- The range of drugs considered in the five studies appraised was not representative of the range of pharmacological interventions employed in clinical practice in New Zealand, suggesting that there is a gap in knowledge on many commonly used medications in the management of people with autism.

Medications are rarely the sole treatment modality for any individuals with autism. As an adjunctive treatment they may be effective with relatively few adverse effects and manageable side effects, although to date evidence is very limited. Many medications that appear promising in small, open-label studies have not yet been studied under reliable experimental conditions, in any age group. In particular, larger sampled, double-blind, placebo-controlled trials are required that address the effectiveness and safety of drug interventions for both short and long-term treatment of adolescents and adults with ASD. Initiatives like the NIMH-funded RUPP Autism Network that permit recruitment across multiple sites may help in this regard (Posey and McDougle 2001), although their focus is currently on children. The use of pharmacotherapy in the management of autism requires a careful assessment of possible benefits and potential risks, in all age groups.

While more research is required on agents that target associated symptoms that interfere with functioning or cause distress, development and evaluation of medications that show promise in treating core symptoms of social and language impairment in ASD should also be a priority.

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- Wirshing, D. A., Wirshing, W. C., Kysar, L., Berisford, M. A., Goldstein, D., Pashdag, J., Mintz, J., et al. (1999). Novel antipsychotics: comparison of weight gain liabilities. *Journal of Clinical Psychiatry*, 60, 358-363.
- World Health Organization (1992). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.
- Zuddas, A., Ledda, M. G., Fratta, A., Muglia, P., & Cianchetti, C. (1996). Clinical effects of clozapine on autistic disorder. *American Journal of Psychiatry*, 153, 738.

Appendix 1: Search strategies

SEARCH STRATEGIES

Medline

- 1 asperger syndrome/ or autistic disorder/ (6411)
- 2 Rett Syndrome/ (763)
- 3 autis\$.mp. (7196)
- 4 kanner's.tw. (39)
- 5 Child Development Disorders, Pervasive/ (578)
- 6 or/1-5 (8128)
- 7 dt.fs. (908568)
- 8 tu.fs. (982011)
- 9 exp Antipsychotic Agents/ (67837)
- 10 exp Psychotropic Drugs/ (223668)
- 11 exp Serotonin Antagonists/ (31267)
- 12 exp Dopamine Antagonists/ (47922)
- 13 secretin/ (5289)
- 14 exp Neurotransmitter Uptake Inhibitors/ (76860)
- 15 exp Vitamin B 6/ (10101)
- 16 "106266-06-2 (Risperidone)".rn. (1633)
- 17 "1393-25-5 (Secretin)".rn. (5289)
- 18 or/7-17 (1413046)
- 19 6 and 18 (880)
- 20 limit 19 to (english language and yr=1980-2003) (693)
- 21 limit 20 to (infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years>) (497)
- 22 (child\$ or infant\$ or paediat\$ or pediat\$.ti. (420572)
- 23 limit 20 to (all adult <19 plus years> or adolescent <13 to 18 years>) (322)
- 24 Adult/ (2375715)
- 25 ADOLESCENT/ (964585)
- 26 20 not (21 or 22) (183)
- 27 20 and (24 or 25) (318)
- 28 23 or 26 or 27 (400)
- 29 letter.pt. (489438)
- 30 28 not 29 (350)
- 31 from 30 keep {SELECTED REFERENCES} (110)

Embase

- 1 autism/ or asperger syndrome/ (3860)
- 2 Rett Syndrome/ (872)
- 3 autis\$.tw. (3930)
- 4 kanner's.tw. (11)
- 5 or/1-4 (5547)
- 6 dt.fs. (851156)
- 7 do.fs. (272237)
- 8 cb.fs. (222993)
- 9 drug effect/ or drug efficacy/ (245705)
- 10 exp Neuroleptic Agent/ (53550)
- 11 exp Psychotropic Agent/ (166079)
- 12 exp Serotonin Antagonist/ (33201)
- 13 exp Dopamine Receptor Blocking Agent/ (22112)
- 14 Pyridoxine/ (4526)

- 15 SECRETIN/ (1838)
- 16 exp "Agents Interacting with Transmitter, Hormone Or Drug Receptors"/ (526734)
- 17 or/6-16 (1353267)
- 18 5 and 17 (1064)
- 19 limit 18 to (human and english language) (915)
- 20 limit 19 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>) (485)
- 21 exp child/ (337149)
- 22 19 not (20 or 21) (430)
- 23 limit 19 to (adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) (336)
- 24 adult/ or exp adolescent/ (1372380)
- 25 19 and 24 (335)
- 26 22 or 23 or 25 (640)
- 27 letter.pt. (238695)
- 28 26 not 27 (587)
- 29 from 28 keep {SELECTED REFERENCES} (119)

Psychinfo

- 1 Rett Syndrome/ (162)
- 2 autis\$.tw. (9911)
- 3 kanner's.tw. (93)
- 4 autism/ or pervasive developmental disorders/ or aspergers syndrome/ or autistic thinking/ (5365)
- 5 or/1-4 (10256)
- 6 drug therapy/ or vitamin therapy/ (49918)
- 7 exp drugs/ (118097)
- 8 6 or 7 (131484)
- 9 5 and 8 (789)
- 10 limit 9 to (english language and yr=1980-2003) (660)
- 11 limit 10 to childhood <birth to 12 years> (300)
- 12 limit 10 to (200 adolescence <age 13 to 17 yrs> or "300 adulthood <age 18 yrs and older>") (303)
- 13 (10 not 11) or 12 (503)
- 14 13 (503)
- 15 limit 14 to human (475)
- 16 from 15 {SELECTED REFERENCES} (120)

Cinahl

- 1 Rett Syndrome/ (44)
- 2 autis\$.tw. (540)
- 3 kanner's.tw. (0)
- 4 Autism/ (651)
- 5 Child Development Disorders/ (549)
- 6 or/1-5 (1255)
- 7 limit 6 to english (1250)
- 8 exp Central Nervous System Agents/ (16062)
- 9 dt.fs. (40065)
- 10 tu.fs. (31367)
- 11 or/8-10 (61738)
- 12 7 and 11 (66)
- 13 from 12 keep {SELECTED REFERENCES} (6)

SEARCHES FROM OTHER SOURCES

In databases and all other sources without controlled vocabulary combinations of the index terms and additional keywords from the above strategies, were used in the search.

Appendix 2: NHMRC levels of Evidence

STUDY QUALITY ASSESSMENT

The strength of the evidence presented in the selected studies will be assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (2000). The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence (see **Table 6**). These are derived directly from the literature identified as informing a particular intervention. The designations of the levels of evidence are shown in **Table 7**.

Table 6. Strength of evidence

Strength of evidence	Definition
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.

* See **Table 7** below

Table 7. Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

* Modified from National Health and Medical Research Council (1999)

Appendix 3: Retrieved excluded articles

Retrieved articles excluded for review (including the reason for exclusion) are described below.

Barthelemy, C., Garreau, B., Leddet, I., Ernouf, D., Muh, J. P., & Lelord, G. (1981). Behavioral and biological effects of oral magnesium, vitamin B6 and combined magnesium: vitamin B6 administration in autistic children. *Magnesium Bulletin*, 3, 150-153.

Mean age = 9 years.

Bouvard, M. P., Leboyer, M., Launay, J. M., Recasens, C., Plumet M.H., Waller-Perotte D., Tabuteau F., & et al. (1995). Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study. *Psychiatry Research*, 58, 191-201.

Mean age = 9 years.

Buitelaar, J. K., van der Gaag, R. J., Cohen-Kettenis, P., & Melman, C. T. M. (2001). A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. *Journal of Clinical Psychiatry*, 62, 239-248.

Patients being treated for aggression and no information is given on whether any have ASD.

Dolske, M. C., Spollen, J., McKay, S., Lancashire, E., & Torbert, L. (1993). A preliminary trial of ascorbic acid as supplemental therapy for autism. *Progress in Neuro Psychopharmacology & Biological Psychiatry*, 17, 765-774.

Mixed child/adolescent sample (range 6 – 19 years), and results not reported separately for those aged over 12 years.

Duker, P. C., Welles, K., Seys, D., Rensen, H., Vis, A., & van den Berg, G. (1991). Brief report: effects of fenfluramine on communicative, stereotypic, and inappropriate behaviors of autistic-type mentally handicapped individuals. *Journal of Autism & Developmental Disorders*, 21, 355-363.

Investigates fenfluramine, an ineligible drug (withdrawn from the market).

Ellaway, C., Williams, K., Leonard, H., Higgins, G., Wilcken, B., & Christodoulou, J. (1999). Rett syndrome: randomized controlled trial of L-carnitine. *Journal of Child Neurology*, 14, 162-167.

Median age = 9 years.

Ellaway, C. J., Peat, J., Williams, K., Leonard, H., & Christodoulou, J. (2001). Medium-term open label trial of L-carnitine in Rett syndrome. *Brain & Development*, 23, S85-S89.

Median age = 10 years.

Fankhauser, M. P., Karumanchi, V. C., German, M. L., Yates, A., & Karumanchi, S. D. (1992). A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *Journal of Clinical Psychiatry*, 53, 77-82.

Sample size is too small (n=9)

Gilman, J. T., & Tuchman, R. F. (1995). Autism and associated behavioral disorders: pharmacotherapeutic intervention. *Annals of Pharmacotherapy*, 29, 47-56.

This commentary/narrative review relates to the treatment of children.

Gordon, C. T., State, R. C., Nelson, J. E., Hamburger, S. D., Rapoport, J. L. (1993). A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Archives of General Psychiatry*, 50, 441-447.

Mean age = 10 years.

Gudarzi, S. S., Yasamy, M., & Akhondzadeh, S. (2002). Cyproheptadine in treatment of autism. *European Psychiatry: the Journal of the Association of European Psychiatrists*, 17, 230-231.

Case report. Sample size is too small (n=2).

King, B. H., Wright, D. M., Handen, B. L., Sikich, L., Zimmerman, A. W., McMahon, W., Cantwell, E., et al. (2001). Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40, 658-665.

Mean age = 7 years.

Kohler, J. A., Shortland, G., & Rolles, C. J. (1987). Effect of fenfluramine on autistic symptoms. *British Medical Journal Clinical Research Ed*, 295, 885.

Investigates fenfluramine, an ineligible drug (withdrawn from the market).

Lelord, G., Muh, J. P., Barthelemy, C., Martineau, J., Garreau, B., & Callaway, E. (1981). Effects of pyridoxine and magnesium on autistic symptoms: initial observations. *Journal of Autism & Developmental Disorders*, 11, 219-230.

Mean age = 9 years.

Lord, C. (2000). Commentary: achievements and future directions for intervention research in communication and autism spectrum disorders. *Journal of Autism & Developmental Disorders*, 30, 393-398.

A commentary/narrative review.

Lott, R. S., Kerrick, J. M., & Cohen, S. A. (1996). Clinical and economic aspects of risperidone treatment in adults with mental retardation and behavioral disturbance. *Psychopharmacology Bulletin*, 32, 721-729.

A before and after open trial with no comparator.

Martineau, J., Barthelemy, C., Garreau, B., & Lelord, G. (1985). Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. *Biological Psychiatry*, 20, 467-478.

Mean age = 8 years.

Martineau, J., Garreau, B., Barthelemy, C., Callaway, E., & Lelord, G. (1981). Effects of vitamin B6 on averaged evoked potentials in infantile autism. *Biological Psychiatry*, 16, 627-641.

Mean age = 7 years.

Martineau, J., Garreau, B., Barthelemy, C., & Lelord, G. (1982). Comparative effects of oral B6 Mg and Mg administration on evoked potentials conditioning in autistic children. In A. Rothenberger (Ed.), *Event-related potentials in children: basic concepts and clinical application* (pp. 411-416). Amsterdam: Elsevier.

Mean age = 7 years.

McDugle, C. J., Naylor, S. T., Cohen, D. J., Aghajanian, G. K., Heninger, G. R., & Price, L. H. (1996a). Effects of tryptophan depletion in drug-free adults with autistic disorder. *Archives of General Psychiatry*, 53, 993-1000.

Not a pharmacological treatment (rather a study of whether depletion of a precursor to 5-HT increases symptoms, which is relevant to why SSRIs may be useful in management of ASD).

McQueen, J. M., & Heck, A. M. (2002). Secretin for the treatment of autism. *Annals of Pharmacotherapy*, 36, 305-311.

This systematic review of the use of secretin relates to children, with all studies not meeting our selection criteria for age.

Molloy, C. A., Manning-Courtney, P., Swayne, S., Bean, J., Brown, J. M., Murray, D. S., Kinsman, A. M., et al. (2002). Lack of benefit of intravenous synthetic human secretin in the treatment of autism. *Journal of Autism and Developmental Disorders*, 32, 545-551.

Mixed child/adolescent sample (range 2 to 15 years), and results not reported separately for those aged over 12 years.

Naruse, H., Nagahata, M., Nakane, Y., Shirahashi, K., Takesada, M., & Yamazaki, K. (1982). A multi-center double-blind trial of pimozide (Orap), haloperidol and placebo in children with behavioral disorders, using crossover design. *Acta Paedopsychiatrica*, 48, 173-184.

Mixed child/adolescent sample (range 3 to 16 years), and results not reported separately for those aged over 12 years.

Owley, T., McMahon, W., Cook, E. H., Laulhere, T., South, M., Mays, L. Z., Shernoff, E. S., et al. (2001). Multisite, double-blind, placebo-controlled trial of porcine secretin in autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 1293-1299.

Age range = 3 to 12 years.

Percy, A. K., Glaze, D. G., Schultz, R. J., Zoghbi, H. Y., Williamson, D., Frost, J. D., Jr., Jankovic, J. J., et al. (1994). Rett syndrome: controlled study of an oral opiate antagonist, naltrexone. *Annals of Neurology*, 35, 464-470.

Mean range = 5 years (treatment group) and 8 years (placebo group).

Ricketts, R. W., Goza, A. B., Ellis, C. R., Singh, Y. N., Chambers, S., Singh, N. N., & Cooke, J. C., 3rd (1994). Clinical effects of buspirone on intractable self-injury in adults with mental retardation. *Journal of the American Academy of Child & Adolescent Psychiatry*, 33, 270-276.

Sample size is too small (n=5).

Ritvo, E. R., Freeman, B. J., Geller, E., & Yuwiler, A. (1983). Effects of fenfluramine on 14 outpatients with the syndrome of autism. *Journal of the American Academy of Child Psychiatry*, 22, 549-558.

Investigates fenfluramine, an ineligible drug (withdrawn from the market).

Ritvo, E. R., Freeman, B. J., Yuwiler, A., Geller, E., Yokota, A., Schroth, P., & Novak, P. (1984). Study of fenfluramine in outpatients with syndrome of autism. *Journal of Pediatrics*, 105, 823-828.

Investigates fenfluramine, an ineligible drug (withdrawn from the market).

Sanchez, L. E., Campbell, M., Small, A. M., Cueva, J. E., Armenteros, J. L., & Adams, P. B. (1996). A pilot study of clomipramine in young autistic children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35, 537-544.

Mean age = 7 years.

Sandler, A. D., Sutton, K. A., DeWeese, J., Girardi, M. A., Sheppard, V., & Bodfish, J. W. (1999). Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. *New England Journal of Medicine*, 341, 1801-1806.

Mean range = 3 to 8 years.

Scifo, R., Cioni, M., Nicolosi, A., Batticane, N., Tirolo, C., Testa, N., Quattropani, M. C., et al. (1996). Opioid-immune interactions in autism: behavioural and immunological assessment during a double-blind treatment with naltrexone. *Annali Dell'Istituto Superiore di Sanita*, 32, 351-359.

Mixed child/adolescent sample (range 7 to 15 years), and results not reported separately for those aged over 12 years.

Stern, L. M., Walker, M. K., Sawyer, M. G., Oades, R. D., Badcock, N. R., & Spence, J. G. (1990). A controlled crossover trial of fenfluramine in autism. *Journal of Child Psychology & Psychiatry & Allied Disciplines*, 31, 569-585.

Investigates fenfluramine, an ineligible drug (withdrawn from the market).

Tanguay, P. E. (2000). Pervasive developmental disorders: a 10-year review. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 1079-1095.

A commentary/narrative review focusing on PDDs generally.

Tolbert, L., Haigler, T., Waits, M. M., & Dennis, T. (1993). Brief report: lack of response in an autistic population to a low dose clinical trial of pyridoxine plus magnesium. *Journal of Autism & Developmental Disorders*, 23, 193-199.

Mixed child/adolescent sample (range 6 to 18 years), and results not reported separately for those aged over 12 years.

Tyrer, S. P., & Moore, P. B. (1993). Eltoprazine improves autistic symptoms in self-injurious mentally handicapped patients. *European Neuropsychopharmacology*, 3, 384.

Sample size is too small (n=8).

Van Bellinghen, M., & De Troch, C. (2001). Risperidone in the treatment of behavioral disturbances in children and adolescents with borderline intellectual functioning: a double-blind, placebo-controlled pilot trial. *Journal of Child and Adolescent Psychopharmacology*, 11, 5-13.

Mean range = 10 years (treatment group) and 11 years (placebo group).

Vanden Borre, R., Vermote, R., Buttiens, M., Thiry, P., Dierick, G., Geutjens, J., Sieben, G., et al. (1993). Risperidone as add-on therapy in behavioural disturbances in mental retardation: a double-blind placebo-controlled cross-over study. *Acta Psychiatrica Scandinavica*, 87, 167-171.

Patients have intellectual disability and no information is given on whether any have ASD.

Yarbrough, E., Santat, U., Perel, I., Webster, C., & Lombardi, R. (1987). Effects of fenfluramine on autistic individuals residing in a state developmental center. *Journal of Autism & Developmental Disorders*, 17, 303-314.

Investigates fenfluramine, an ineligible drug (withdrawn from the market).

Appendix 4: Included appraised articles

INCLUDED APPRAISED SECONDARY ARTICLES

Barnard, L., Young, A. H., Pearson, J., Geddes, J., & O'Brien, G. (2002). A systematic review of the use of atypical antipsychotics in autism. *Journal of Psychopharmacology*, 16, 93-101.

Di Martino, A., & Tuchman, R. F. (2001). Antiepileptic drugs: affective use in autism spectrum disorders. *Pediatric Neurology*, 25, 199-207.

Kleijnen, J., & Knipschild, P. (1991). Niacin and vitamin B6 in mental functioning: a review of controlled trials in humans. *Biological Psychiatry*, 29, 931-941.

Nye, C., & Brice, A. (2002). Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database of Systematic Reviews*.

Patel, N. C., Yeh, J. Y., Shepherd, M. D., & Crismon, M. L. (2002). Secretin treatment for autistic disorder: a critical analysis. *Pharmacotherapy*, 22, 905-914.

Pfeiffer, S. I., Norton, J., Nelson, L., & Shott, S. (1995). Efficacy of vitamin B6 and magnesium in the treatment of autism: a methodology review and summary of outcomes. *Journal of Autism & Developmental Disorders*, 25, 481-493.

Toren, P., Laor, N., & Weizman, A. (1998). Use of atypical neuroleptics in child and adolescent psychiatry. *Journal of Clinical Psychiatry*, 59, 644-656.

INCLUDED APPRAISED PRIMARY ARTICLES

McDougle, C. J., Holmes, J. P., Carlson, D. C., Pelton, G. H., Cohen, D. J., & Price, L. H. (1998). A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Archives of General Psychiatry*, 55, 633-641.

McDougle, C. J., Naylor, S. T., Cohen, D. J., Volkmar, F. R., Heninger, G. R., & Price, L. H. (1996b). A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Archives of General Psychiatry*, 53, 1001-1008.

Remington, G., Sloman, L., Konstantareas, M., Parker, K., & Gow, R. (2001). Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *Journal of Clinical Psychopharmacology*, 21, 440-444.

Willemsen-Swinkels, S. H. N., Buitelaar, J. K., Nijhof, G. J., & van Engeland, H. (1995). Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults: double-blind placebo-controlled studies. *Archives of General Psychiatry*, 52, 766-773.

Zarcone, J. R., Hellings, J. A., Crandall, K., Reese, R. M., Marquis, J., Fleming, K., Shores, R., et al. (2001). Effects of risperidone on aberrant behavior of persons with developmental disabilities: I. A double-blind crossover study using multiple measures. *American Journal on Mental Retardation*, 106, 525-538.