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

Technical Document

Shoumitro Deb, MBBS, FRCPsych, MD, Clinical Professor of Neuropsychiatry and Intellectual Disabilities
and Gemma L. Unwin, BSc(Hons).

University of Birmingham,
Division of Neuroscience,
Department of Psychiatry, UK.

Acknowledgments: Thanks to the Guideline Development Group members – Gill Bell, Sabyasachi Bhaumik, David Branford, Rob Chaplin, David Clarke, Chris Dale, Caroline Lee, Suzanne Robinson, Ashok Roy, Florence Simon, Ray Smart, Biza Stenfert Kroese, Caron Thomas, Miriam Wilcher, and Linda Woodcock

www.LD-Medication.bham.ac.uk

November 2006

Supported by
BIG LOTTERY FUND
UNIVERSITY OF BIRMINGHAM
The Royal College of Psychiatrists
Let Wisdom Guide
MENCAP
Understanding learning disability

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

Technical Document Section 3.1: Systematic Reviews: Introduction

Shoumitro Deb, MBBS, FRCPsych, MD, Clinical Professor of Neuropsychiatry and Intellectual Disabilities, Gemma Unwin, BSc(Hons), Rivashni Soni, MBChB, MSc (Clinical Epidemiology), Sundip Sohanpal, BSc(Hons), MRes & Laure Lenotre, BSc(Hons).

University of Birmingham,
Division of Neuroscience,
Department of Psychiatry, UK.

www.LD-Medication.bham.ac.uk

November 2006

Supported by
BIG LOTTERY FUND
UNIVERSITY OF BIRMINGHAM
The Royal College of Psychiatrists
Let Wisdom Guide
MENCAP
Understanding learning disability

Identifying the evidence on efficacy

Evidence on the efficacy of medication used to manage behaviour problems in adults with a learning disability (LD) was identified. The process involved a systematic reviewer, a second reviewer and an information specialist. The process of identifying the evidence was an iterative one and feedback was provided at all stages by the GDG.

Preliminary searches:
Terms used to describe a learning disability and behaviour problems as well as a list of possible medications were investigated. A list of terms was compiled for the GDG (see Appendix 2).

Early searches:
During the early stages of the proper search, it was decided that the search would be as inclusive as possible so as not to miss any important papers. As a result, search terms were kept broad and most terms were exploded in the different databases. It was also decided that most terms would be searched as both MeSH terms and key/ text words.

Restrictions on the search:
Initially, the search was restricted to all trials, in adults aged 18 and over, from 1990 to the current date. Subsequently the original database searches were extended to include any relevant controlled trials reported prior to 1990 and all relevant RCTs were also looked into by hand searching journals and cross-referencing other papers.

As far as language was concerned, all papers that had an abstract published in English were searched. If the paper appeared relevant from the abstract, an attempt was made to obtain the full text.

The following electronic databases were searched:

- Medline
- Embase
- PsycInfo
- Cinahl

Once the scope had been finalised, in the process of answering the clinical questions as defined by the GDG members, the following steps were employed:

- Firstly, a search was conducted for reviews available in the literature looking at the efficacy of the treatment of behaviour problems in individuals with a LD. Many reviews with various levels of quality were retrieved.

- It was then decided to limit the search to systematic reviews. This search revealed four relevant systematic reviews.
- The preliminary search for primary trial evidence was then commenced.
- Finally, a search strategy was devised to enable the identification of the best available evidence relating to the efficacy of different treatments discussed in the guideline.
- The first interest was directed towards antipsychotic medication.
- This strategy was modified and replicated to identify evidence on the other classes of medication.

Identification of reviews on the use of medication in the management of behaviour problems in adults with a learning disability

Inclusion criteria

In order to merit inclusion in this first search, the studies had to meet the following criteria:

- The effectiveness of medication had to be explored in the management of a behaviour problem
- Participants had to have a learning disability with or without a psychiatric disorder
- Any medication treatment could have been used
- The participants had to be adults of 18 years of age or older
- Articles had to be from within the past 15 years
- An abstract in English was required.

Databases used

Embase and Medline (via Ovid gateway)

- Medline (1990 to 2nd week of May 2004)
- Embase (1990 to 3rd week of May 2004)

Results

- Embase: 3422
- Medline: 538

} 3960 hits

Total without duplicates: 3742 hits

These articles were divided into two:

- 2000-2004 1769 hits ► these were looked into more closely
- 1990-1999 1973 hits

(Search of PsycInfo (via Dialog Datastar gateway) retrieved 500 papers but these were not explored due to the lack of time).

A close inspection revealed 15 relevant reviews, which were presented to the GDG members.

Identification of systematic reviews on the use of medication in the management of behaviour problems in adults with a learning disability

Inclusion criteria

The inclusion criteria was same as in the previous search but this time covering the years 1999 to October 2005.

Databases used

- Embase (1999 to 43rd week of 2005)
- Medline (1999 to week 1 October 2005)
- PsycInfo (1999 to week 2 October 2005)
- Cinahl (1999 to week 2 October 2005)

Embase, Medline and Cinahl were searched via Ovid and PsycInfo via Dialog Datastar.

Results

- Embase 415
- Medline 51
- PsycInfo 7
- Cinahl 14

} 487 hits

Total without duplicates: 451 hits

After scanning through all these, 3 relevant systematic reviews were identified.

It was agreed by the GDG that the systematic reviews available were not answering the clinical questions. Therefore, it was decided that a full systematic review should be carried out using search terms that were discussed with the GDG members.

Preliminary search of all types of medication

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

The purpose of this search was to find papers within 1994 to 2005 of trials of any size.

Search strategy

The terms used in this search were discussed with the GDG members at an earlier stage. The search strategy used by Brylewsky & Duggan (2004; available in The Cochrane Library - ISSN 1464-780X) in their systematic review on antipsychotics was adopted; as this systematic review appeared to be the closest to the present topic. The search strategy used in the 'Self-Harm NICE Guideline' (www.nice.org.uk/page.aspx?0=cg016niceguideline) was also looked into. An Information Specialist checked the search.

Inclusion criteria

Subsequent to discussion with the GDG, the following criteria was decided for the selection of relevant studies for inclusion in this review:

- It was decided that studies including less than 10 individuals would not be included in this systematic review but kept aside in a box for future reference.
- The target population of the study had to be individuals with a learning disability (LD) including those with borderline intelligence, or there had to be separate information for the relevant population if non-LD individuals were also included in the study.
- The intervention had to be a medication or supplement used to control a behaviour problem.
- A comparator group did not have to be present.
- If baseline and outcome data relating to the target behaviour were not reported before and after the intervention respectively, the paper was excluded.
- The participants had to be aged 18 years or over or data had to be available separately on individuals within this age group.

Databases used

- PsycInfo (1994 to 4th week of July 2004)
- Medline (1994 to 4th week of July 2004)
- Embase (1994 to 30th week of 2004)
- Cinahl (1994 to 4th week of July 2004)

Results

Each of the databases retrieved the following number of citations:

- PsycInfo 223
- Medline 157
- Embase 771
- Cinahl 18

1169 hits

Total without duplicates: 933

This preliminary search identified 72 potential papers including some of which were case studies that appeared relevant from abstract inspection. This search then led on to a more thorough search of individual medication groups.

Searches for individual classes of medication

Identification of primary trials on the use of individual classes of medication in the management of behaviour problems in adults with a learning disability

Search strategy

The objective of these searches was to determine the number of primary trials relating to the use of different classes of medication for the treatment of behaviour problems in adults with a learning disability. Initially a search was conducted to identify studies exploring the efficacy of antipsychotic medication. Following discussion with the GDG members, the search was separately adapted to other classes of medication namely antidepressants, mood stabilisers/ antiepileptics, anti-anxiety/ benzodiazepines/ beta-blockers, opioid antagonists, psychostimulants and finally vitamins and any other types of medication intervention that could not be allocated to the above groups.

In the first instance, a comprehensive electronic database search was carried out selecting all types of trials dating from 1990 onwards. Following this, cross-referencing of pertinent reviews and a hand search of articles was carried out to check for any appropriate articles which may not have been indexed in the databases searched. This latter stage indicated that there appeared to be relevant RCTs for adults before 1990 and children after 1990. Therefore, each of the electronic database searches was extended and two further searches were performed for each of the classes of medication. As controlled trials are recognised as providing 'gold standard' evidence, these additional searches were limited to include controlled trials only relevant to adults dating pre-1990 and controlled trials only in children from 1990 onwards.

In all three searches, in order to limit any bias due to language limitation, it was decided to include all papers with an abstract in English even if the full text was in another language. An Information Specialist advised in all the searches.

The specific criterion for inclusion of studies in each of the searches were as follows:

Search 1: Identification of all types of trials (including RCTs to case series) limited to the time period 1990 to 2004 – this search was updated on October 2005

Types of studies
Any experimental study where medication is one of the interventions used to treat behaviour problems.

Types of participants
All individuals 18 years of age and older with a learning disability (IQ below 70 or as defined by the author) and exhibiting a behaviour problem (as defined by the author) in the form of self-injury, aggression towards others and any other type of behaviour problems (e.g. damage to property etc.). Papers including participants presenting with a co-morbid psychiatric diagnosis, Pervasive Developmental Disorder (PDD), Attention Deficit Hyperactivity Disorder (ADHD), autism spectrum or personality disorder were included if the study intervention was primarily and specifically to treat a behaviour problem.

Sample size
A sample size of ten or more participants.

Types of interventions
All medications stated in the British National Formulary (BNF; September, 2004) that are presently used to treat behaviour problems in adults with a learning disability.

Types of outcome measures
Any outcome related to the behaviour before and after the intervention.

Search 2: Identification of controlled trials in adults covering the period before 1990

Types of studies
Any randomised or non-randomised controlled trials where medication is used to treat a behaviour problem.

Participants, sample size, interventions and outcome measures as in search one.

Search 3: Identification of controlled trials covering the period 1990 to June 2005 to include participants younger than 18 years old

Types of studies
Any randomised or non-randomised controlled trials where medication is used to treat a behaviour problem.

Types of participants
As in searches 1 and 2 but this time only children and adolescents under the age of 18 years were considered. Studies in which participants presented with autism were considered if at least 50% of the sample also had a learning disability.

Sample size, interventions and outcomes measures as in search one.

Databases used

- PsycInfo
- Medline
- Embase
- Cinahl

Search terms

The reviewers used search terms that were discussed with the GDG members and adapted from the strategy used by Brylewski & Duggan (2004). The search strategy was adapted to each of the databases mentioned above and to each of the classes of medication, but the basis of each search consisted of the following 84 items:

1.exp behavior/
2. exp aggression/
3. exp coprophagy/
4. exp feces incontinence/
5. exp enuresis/
6. exp obsession/
7. exp paranoia/
8. exp automutilation/
9. exp SUICIDE/ or exp ASSISTED SUICIDE/ or exp SUICIDE ATTEMPT/
10. exp crying/
11. exp drinking behavior/
12. exp habit/
13. exp impulsiveness/
14. exp compulsion/
15. exp self stimulation/
16. exp masturbation/
17. exp social isolation/
18. exp stereotypy/
19. crime/ or exp forgery/ or exp homicide/ or exp infanticide/ or exp sexual crime/ or exp rape/
20. exp Sexual Abuse/ or exp Child Abuse/
21. exp VIOLENCE/ or exp DOMESTIC VIOLENCE/
22. exp partner violence/
23. exp runaway behavior/
24. exp coprophagy/
25. exp hyperphagia/
26. exp pica/
27. exp echolalia/
28. exp mutism/
29. exp restlessness/
30. (aggression$ adj3 (behav$ or disorder$)).tw.
31. ((violen$ or self-injur$ or self injur$) adj3 behav$).tw.
32. (self-injury$ or self injur$).tw.
33. aggression$.tw.
34. ((damag$ or destruct$) adj4 propert$).tw.
35. ((problem$ or disorder$) adj2 (behavior$ or behaviour$)).tw.
36. (challenging adj1 (behaviour$ or behavior$)).ti.
37. verbal aggression$.tw.
38. threat$.tw.
39. screaming$.tw.
40. excessive noise$.tw.
41. temper tantrum$.tw.
42. polydipsia$.tw.
43. pica$.tw.
44. smearing faeces$.tw.
45. antisocial habit$.tw.
46. spitting$.tw.
47. inappropriate sexual behaviour$.tw.
48. skin picking$.tw.
49. nail biting$.tw.

50. head banging$.tw.
51. rocking$.tw.
52. (agonistic$ or disturb$ or hostil$ or agitation$ or anger$ or angry$ or rage$ or bizarre$ or harass$ or intimidation$ or agress$ or danger$ or attack$ or threat$ or abus$ or combative$ or assault$ or disrupt$).tw.
53. or/1-52
54. exp mental deficiency/
55. exp cat cry syndrome/
56. exp de lange syndrome/
57. exp down syndrome/
58. exp x linked mental retardation/
59. exp adrenoleukodystrophy/
60. exp coffin lowry syndrome/
61. exp fragile x syndrome/
62. exp lesch nyhan syndrome/
63. exp menkes syndrome/
64. exp hunter syndrome/
65. exp pyruvate dehydrogenase complex deficiency/
66. exp rett syndrome/
67. exp prader willi syndrome/
68. exp rubinstein syndrome/
69. exp wagr syndrome/
70. exp williams beuren syndrome/
71. exp mental patient/
72. (mental$ adj3 (difficult$ or deficien$ or handicap$ or retard$ or impair$ or disable$ or disability$ or incapacity$ or subnormal$)).tw.
73. (learning adj3 (difficult$ or deficien$ or handicap$ or retard$ or impair$ or disable$ or disability$ or incapacity$ or subnormal$)).tw.
74. (intel$ adj3 (difficult$ or deficien$ or handicap$ or retard$ or impair$ or disable$ or disability$ or incapacity$ or subnormal$)).tw.
75. (development$ adj3 (difficult$ or deficien$ or handicap$ or retard$ or impair$ or disable$ or disability$ or incapacity$ or subnormal$)).tw.
76. (cognitiv$ adj3 (difficult$ or deficien$ or handicap$ or retard$ or impair$ or disable$ or disability$ or incapacity$ or subnormal$)).tw.
77. (learning adj3 difficult$).tw.
78. down$ syndrome$.tw.
79. (fragile adj3 syndrome$).tw.
80. phenylketonuria$.tw.
81. (subnormal$ adj3 intel$).tw.
82. oligophren$.tw.
83. differently abled.tw.
84. or/54-83

These phrases were entered into the databases with the addition of more specific terms relevant to each of the classes of medication, these will be mentioned later under each of the individual searches. Once the search of each database was completed, all citations were individually copied into Endnote libraries where duplicate citations were removed after being scanned. For the purposes of Search 2, the limits for Search 1 were reset to distinguish controlled trials before 1990. In addition, for the purposes of Search 3 the limits of Search 1 were reset to identify controlled trials from 1990 onwards where the sample included children and/or adolescents.

Selection criteria for relevant studies

A breakdown of each of the selection processes are described in detail under each of the searches, but typically at the outset, after all duplicates were removed, those citations remaining were scanned on the basis of their title and those that fell outside the scope of the present review were eliminated. In all the medication classes, those citations that were removed at this stage largely comprised the following:

- Trials done on animals (mice, monkeys, hamsters, rats etc.)
- Trials on cancer treatment and leukaemia
- Trials on HIV and AIDS
- Trials on anaesthesia and anaesthetic agents
- Trials on interventions used in dental treatment
- Trials on fractures and bone loss
- Trials on substance abuse and recreational drug use
- Trials on smoking cessation
- Trials on other classes of medication not applicable to the class being reviewed
- Trials on the effects of substances in unborn babies, healthy volunteers, children and veterans
- Trials on drug molecular activity
- Trials on the effect of medication on human performance
- Trials on sleep studies
- Trials on cognitive behavioural therapy, compulsive buying, obsessive compulsive disorder, decision making, hormone replacement therapy, pregnancy and menopause
- Trials on Alzheimer's disease, dementia, depression, multiple sclerosis, stroke, traumatic brain injury, diabetes, hypertension, tuberous sclerosis, myocardial infarction and coronary heart disease
- Surveys on the use of medication, quality of life, prevalence and compliance studies
- Trials on electroconvulsive therapy
- Trials on medication not included in the BNF
- Reviews, audits and validation papers looking at the efficacy of tools.

At the next stage, the remaining abstracts were checked in order to identify those citations that were clearly not relevant to the clinical question and could thus be excluded. The following are examples of reasons for excluding papers at this stage:

- Trials on the assessment of cognitive function in people with schizophrenia, depression or in healthy volunteers
- Trials on physical co-morbidity in schizophrenia or phobias
- Trials on psychomotor retardation
- Trials on psychiatric disorders with no behavioural symptoms
- Trials on receptors (e.g. muscarinic, nicotinics etc.)
- Trials on stuttering
- Trials on policies and the use of diverse services (e.g. prison)
- Studies looking at the methodology of drug trials or validation of questionnaires
- Trials on educational programs
- Studies relating to costs
- Trials on gender differences
- Trials on nursing care
- Trials on medication withdrawal symptoms or overdose

- Trials where no intervention was involved
- Extractions from books

Thereafter, any missing abstracts were retrieved for the remaining citations and these were scrutinized using inclusion/exclusion criteria forms (see Appendix 3) previously developed and piloted by the two reviewers. The GDG members agreed the criterion for these forms. Where disagreements arose between the two reviewers, these were settled by discussion where a consensus was reached. Where a consensus could not be reached, a third reviewer's opinion was sought. Studies were excluded if they failed to meet the criteria as determined by the reviewers. The full text was obtained for the others because there was not enough information contained within the abstracts. It was also necessary to obtain further information for some of the papers by contacting the authors. In the interim, some citations were kept aside in a box for future reference due to relevance but small sample size. In cases where it was not possible to get hold of the abstracts or full texts, the GDG members assisted in deciding whether certain studies were to be included or excluded. Once all the information was available, all papers were again scrutinized using the criteria forms by two reviewers and again, disagreements were settled by discussion.

Data extraction, quality assessment and analysis of results

Data extraction and quality assessment was carried out for those papers that met the eligibility criteria for the review under which they were considered. One reviewer extracted all the data on pre-piloted data extraction forms (see Appendix 4). The quality of each paper was concurrently appraised using quality control forms relevant to the type of study (see Appendix 5). It was decided that RCTs would be rated against the Jadad quality assessment criteria (Jadad et al. 1996) as well as additional criteria developed in discussion with the GDG for controlled trials in general. Studies found in Search 3 were only assessed against the Jadad criteria because children were not of primary interest within this guideline. Criteria for the quality assessment forms for case series studies were also developed following discussion with the GDG. Studies were additionally allocated evidence category ratings which further determined the quality of the type of methodology used whereby a rating of I represented a RCT, II – a controlled trial without randomisation and III – other non-experimental study such as case series. Thus, any study that was not controlled was subjected to the case series quality assessment criteria. These quality control forms had also been developed and piloted by two reviewers at an earlier stage. The inclusion/exclusion, data extraction, quality control forms and evidence category ratings were all adapted from the HTA NICE guideline (www.nice.org.uk). All data were then crosschecked when entered into an electronic database by a second reviewer.

On completion of the electronic and hand searches, all studies that met the inclusion criteria were summarised using a qualitative narrative approach. The resulting evidence base along with the individual searches and details on

the number of papers found - included and excluded, are discussed separately in the next sections.

Furthermore, three lists were compiled for each of the seven classes of medication under review. These lists are presented under the reference sections of the systematic review but fundamentally consist of those studies that underwent the inclusion/exclusion criteria. The first list under each class of medication refers to those studies which met the eligibility criteria and for which quality assessments were carried out. The second lists include those studies that were relevant to the review but had less than 10 participants. The third list is of those studies that were excluded based on criteria scrutiny on either their abstracts or full texts. In addition, references are also provided for the findings of searches 2 and 3.

Appendix 1: Glossary

This has been modified from the NICE's information for national collaborating centres and guideline development groups *(NICE 2001)* and from the Clinical Practice Guidelines for the Short-Term Management of Violent (Disturbed) Behaviour in Adult Psychiatric In-patient and Accident and Emergency Settings. It is also partially based on the *Clinical Epidemiology* glossary by the Evidence Based Medicine Working Group (http://www.med.ualberta.ca/ebm/define.htm#top), the Medline glossary, from which terms relating to the search strategy itself were obtained (http://www.med.ualberta.ca/ebm/medglos.htm) and *A glossary for evidence based public health* (J Epidemiol Community Health 2004; 58:538-545). Some of the glossary was also partially adapted from SIGN's 'A guideline developers' handbook' (http://www.sign.ac.uk/guidelines/fulltext/50/annexg.html).

Bias
May result from flaws in the design of a study or in the analysis of results.

Blind(ed) study
A study in which observer(s) and/or participants are kept ignorant of the group to which the participants are assigned, as in an experimental study, or of the population from which the participants come, as in a non-experimental or observational study.

Boolean search
This refers to a combination of search statements or sets using the logical operators "OR" to expand a search and "AND" to restrict a search to articles that contain two or more specified elements together.

Case series
Description of several cases of a given disease, usually covering the course of the disease and the response to treatment.

Cinahl
An electronic database of nursing and allied health literature from 1982 to present.

Cochrane Collaboration
An international organisation in which people retrieve, appraise and review available randomised controlled trials. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of issues and is available electronically.

Cohort study
A 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, or exposed in different degrees, to a factor or factors hypothesised to influence the probability of occurrence of a given disease or other outcome.

Co-morbidity
Co-existence of a disease or diseases in a study population in addition to the condition that is the subject of study.

Comparison (comparator) group
Any group to which the index group is compared. Usually synonymous with the control group.

Confidence interval (CI)
The range of numerical values in which we can be confident that the population value being estimated were found. Confidence intervals indicate the strength evidence; where confidence intervals are wide they indicate less precise estimates of effects.

Confounding variable (confounder)
A variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation. A confounding variable may be due to chance or bias. Unless it is possible to adjust for confounding variables, their effects cannot be distinguished from those of the factor(s) under study.

Control group
A group of participants recruited into a study that receives either no treatment, treatment of known effect, or placebo, in order to provide a comparator for a group receiving an intervention.

Effectiveness
The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do. Clinical trials that assess effectiveness are sometimes called management trials.

Efficacy
The extent to which an intervention produces a beneficial result under ideal conditions. Clinical trials that assess efficacy are sometimes called explanatory trials and are restricted to participants who fully co-operate.

Embase
An electronic database of biomedical and pharmaceutical scientific literature.

Exclusion Criteria
Conditions that preclude entrance of candidates into an investigation even if they meet the inclusion criteria.

Explode

Permits simultaneous searching of both a broad subject and the narrower subjects classed under it (e.g., searching "Antiviral Agents" will retrieve articles on antiviral agents in general, new antiviral agents not yet assigned a MeSH heading, plus individual drugs such as "Acyclovir" or Zidovudine" classed as antiviral agents in Medline). Because indexing norms require that the most specific subject heading available be applied, normally an article indexed under the specific heading would not also be indexed under the broader heading; thus, searching only the broad subject would result in lost references, which have been indexed under the more specific heading.

Fields
These are labelled divisions of a Medline record; most fields are directly searchable, separately or as specified in an "expert search", set off by periods (e.g., random$.ti,ab,sh,pt. or alberta.ti,ab,sh,in.). Medline fields include:

- AU=Author
- TI=Title of article
- SO=Journal title, volume, issue, pages and year of publication
- AB=Abstract (present in about 2/3 of Medline references) Note: abstracts are reprinted from the original paper if the original had no abstract, there will be no abstract in Medline)
- IN=Institution
- SH=List of subject headings under which the article is indexed, including subheadings
- UI=Unique Identifier, an accession number applied to each Medline record as it is entered
- PT=Publication Type (e.g., review, randomized controlled trial, clinical trial, meta-analysis, practice guideline, etc.)
- RN=Chemical Abstracts Registry Number (useful for searching new or obscure drugs or toxic agents)
- RW=Registry Number Word (used for searching portions of chemical names, new or obscure drugs)

Follow-up
Observation over a period of time of an individual, group of population whose relevant characteristics have been assessed in order to observe changes in health status or health-related variables.

Gold standard
A method, procedure or measurement that is widely accepted as being the best available.

Inclusion criteria
Conditions which permit entrance of candidates into an investigation if they meet the inclusion criteria.

Intention to treat analysis
An analysis of a clinical trial where participants are analysed according to the group to which they were randomly allocated initially, regardless of whether or

not they had dropped out, fully complied with the treatment, or crossed over and received the other treatment.

Limit
Limit places broad restrictions applicable to existing search sets; includes designations such as:

- Human, animal (and types of animal)
- English or other languages
- Publication types (e.g., review, randomised controlled trial, clinical trial, meta-analysis, practice guideline, etc.)
- Age groups
- Gender
- Journal subsets (including AIM journals, Nursing Journals, and Dental Journals)
- Year of publication
- Latest update

Mapping
This is a computer process whereby the search system matches a term entered to the closest subject headings in the database.

Medline
An electronic index to the contents of biomedical and health sciences journals published since 1966. Medline includes Index Medicus, the Index to Dental Literature, and the International Nursing Index.

MeSH
Medical Subject Headings, the thesaurus for Medline; a controlled vocabulary providing consistent terminology for concepts covered by the database.

Number Needed to Treat (NNT)
The number of people who must be exposed to an intervention before the clinical outcome of interest occurred; for example, the number of people

Objective measure
A measurement that follows a standardised procedure that is less open to interpretation by potentially biased observers and study participants.

Post-qualification
This is used with existing broad subject heading search statements to focus the search and reduce the number of postings while increasing their relevance. To restrict a subject heading to focus, preface the set number with an asterisk (*) (e.g., if set 1 is Tuberculosis and you wish to find only papers where this is a central focus, create a new search statement by entering "*1"). To focus a search by the use of subheadings after the set has been created, enter the set number followed by a forward slash and the two-letter subheading designators desired (e.g., if set 1 is Tuberculosis, and you wish to restrict your search to "prevention and control" and "transmission", enter "1/pc,tm").

Prospective study
Study design where one or more groups (cohorts) of individuals who have not yet had the outcome event in question are monitored for the number of such events, which occur over time. Prospective studies may be of several types, including cohort or randomised controlled trials.

PsycInfo
An electronic abstract database of psychological literature from the 1800s to present.

Randomised controlled trial (RCT)
A clinical trial in which the treatments are randomly assigned to subjects. The random allocation eliminates bias in the assignment of treatment to patients and establishes the bias for the statistical analysis.

Restrict to focus
Is a choice offered following selection of a subject heading to be searched; choosing "all documents" at this point will retrieve all references indexed with a particular subject heading; choosing "Restrict to focus" will retrieve only references where this concept is a central focus of the article. Note that some MeSH headings, such as geographical names or headings relating to experimental design, are almost never designated under "restrict to focus".

Retrospective study
Study design in which cases where individuals who had an outcome event in question are collected and analysed after the outcomes have occurred.

Scope Note
This defines a particular MeSH heading and explains its parameters, provides synonyms covered by the heading, year a MeSH heading was adopted by Medline, previous indexing for the MeSH heading, and cross references to other possibly relevant MeSH headings.

Selection Bias
Bias in assignment or a confounding variable that arises from study design rather than by chance. These can occur when the study and control groups are chosen so that they differ from each other by one or more factors that may affect the outcome of the study.

Subheadings
These are generic terms to narrow and focus a MeSH subject-heading search; on OVID systems, the scope of each subheading is presented on the right hand panel of the search screen where subheadings are selected. One or several headings may be selected at a time, and "all subheadings" may be selected.

Systematic review
Research that summarizes the evidence on a clearly formulated question according to a predefined protocol using systematic and explicit methods to

identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Textword
These are exact words found in the title and/or abstract fields; useful for searching if no MeSH heading exists for a specific concept. Textword searching requires the use of synonyms and bypasses the mapping feature that allows "restrict to focus" and subheading selection. Generally, prefer thesaurus searching (i.e., using the subject or MeSH headings).

Tree
These are classified listing of subject headings, showing broader and narrower concepts. Can be searched selectively using the "Tools" function on OVID.

Truncation
This means searching for all variations based on a word stem. The truncation symbol on OVID is $. (e.g., predict$=predict, predicts, prediction, predicting, etc.).

Validity
The extent to which a variable or intervention measures what it is supposed to measure or accomplish.

Internal validity: of a study refers to the integrity of the design and is the degree to which the results of a study are correct for the sample of people being studied.
External validity (generalisability): of a study refers to the appropriateness by which its results can be applied to non-study patients or populations.

Appendix 2: Preliminary search terms

LIST FOR DISABILITIES TO BE DEFINED	ANTIPSYCHOTICS	ANTIDEPRESSANTS	ANTICONVULSANTS
Learning disability	1. Atypical Antipsychotics	1. Heterocyclic Antidepressants	1. Barbituates
Learning disabled	Clozapine	Imipramine	Primidone
Intellectual disability	Risperidone	Clomipramine	2. Hydantoins
Intellectually disabled	Olanzapine	Amitryptaline	Phenytoin Sodium
Mental retardation	Quetiapine	Amoxapine	Fosphenytoin Sodium
Mentally retarded	Amisulpride	Lofepramine	3. Succinimides
Mentally challenged	2. Phenothiozine	Maprotiline	Ethosuxamide
Mental handicap	Methotrimeprazine maleate (group I)	Doxepin	4. Benzodiazepines
Mental Impairment	Chlorpromazine (group I)	Trimipramine	Clonazepam
Sub-average intelligence	Thioridazine (group II - piperidine)	2. SSRI	Diazepam
Developmental disability	Perphenazine (group III – piperazine)	Sertraline	Lorazepam
Developmental disabilities	Fluphenazine (group III – piperazine)	Escitalopram	5. Dibenzazepine
	3. Others	Paroxetine	Carbamazepine
LIST FOR BEHAVIOUR SYMPTOMS	Haloperidol (Butyrophenone)	Fluvoxamine	Oxcarbazepine
Aberrant	Pimozide (diphenylbutylpiperidine)	Venlafaxine	6. Carboxylic Acid
Aggression	Loxapine (dibenzoxazapine)	Fluoxetine	Sodium Valproate
Aggressive	Zotepine (tricyclic dibenzothiepine)	Citalopram	7. Carbonic Anhydrase
Attention-Deficit Hyperactivity Disorder	MOOD STABILISERS	3. Other	Acetazolamide
Behaviour disorder	Lithium	Trazadone	8. Triazine
Behavioural problem	Carbamazepine	PSYCHOSTIMULANTS	Lamotrigine
Challenging	Sodium Valproate	Methylphenidate	9. GABA anologue
Disruptive	BETA-BLOCKERS	Dexamphetamine	Gabapentin
Hyperactivity	1. Non-selective beta-blockers	HORMONAL MEDICATION	Vigabatrin
Offender	Propranolol	Medroxyprogesterone acetate	Tiagabine
Offending	Pindolol	Oestrogen	Piracetam
Self mutilation	Timolol	OPIOD ANTAGONISTS	
Self-injury	Nadolol	Naloxone	
Stereotyped	Labetolol	Naltrexone	
Stereotypical	2. Selective beta-blockers	DRUG	
	Metoprolol	**Other**	
	Acebutolol	Buspirone	
	Atenolol	Clonidine	
	Bisoprolol		

Appendix 3: Inclusion and exclusion criteria

Author:
Year:
Reviewer:

Study Design: Is this study a RCT or non-randomised trial with a concurrent group of a similar population or non-randomised trial with no concurrent population ?	Y	N	U
Population: Is the population described as being people with a learning disability (including borderline IQ) or is there separate information on those with LD/borderline LD?	Y	N	U
Intervention: Is the intervention any medication/supplement (including dietary changes) that is used to control a behaviour problem?	Y	N	U
Comparator: Is the comparator a placebo/non-medication intervention (e.g. behaviour therapy) /no treatment or another medication/supplement (including dietary changes)?	Y	N	U
Exclusion:			
1. Is there a report on outcomes related to behaviour before and after the intervention? (Including adverse events related to the treatment of the behaviour)	Y	N	U
2. Is the age of participant's ≥ 18 years or is there separate data for those 18 years old and over?	Y	N	U
3. Does the sample size of those meet our eligibility criteria for the review ≥10?	Y	N	U

If all yes, include for review.
If all yes but sample size < 10, put in box.

Appendix 4: Data extraction form

Review Date: _____
Reviewers Initials: _____

Trial Details	Author	
	Year of Publication	
	Journal Name	
	Volume, Issue, Page	
	Drug Name	
	Status (published, ongoing etc)	
Trial Design (please attach relevant quality assessment form)	Type of Study	
	Retro/prospective	
Sample Population	Eligibility criteria	
	Number	
	Setting	
Study Group	Number of cases	
	Average Age	
	Percent male	
	IQ range and percent in each range (if mentioned)	
	Diagnosis	
	Co-morbid illness (physical, other)	
Control group	(If no, go to target	Y N

	behaviour)	
	Number of controls	
	Average Age	
	Percent males	
	IQ range and percent in each range (if mentioned)	
	Diagnosis	
	Co-morbid illness (physical, other)	
Target behaviour		

Intervention/Comparator

	Intervention	Comparator
Name of Treatment		
Starting Dose		
Average Dose		
Max dose		
Mode of administration		
Length of time on treatment		
Any adjuvant therapy?		
Follow-up intervals		
Length of follow-up		
Medication used previously and duration of treatment		
Washout-period or initiation of study medication		

Comments:

……

……

……

……

Outcomes

Primary Outcomes	
Secondary outcomes (excl. adverse events)	
Other (including adverse events)	

How were outcomes measured?

……

……

……

……

……

……

……

……

Who did the outcome assessment?

……

……

When were outcomes assessed? (time period)

……

……

Results

Overall Comments (including comment on quality)

……

……

……

……

……

……

……

……

……

……

……

……

Appendix 4: Quality assessment forms

JADAD RCT Quality Assessment Form

Reviewer's Initials:
Authors:
Pub Year:

1. **Randomisation**	Y	N	U
- Was the study described as randomised? *(this includes the use of words such as randomly, random, randomised)*	☐	☐	
- Was the method used to generate the sequence of randomisation described and was it adequate?	☐	☐	☐
2. **Blinding**			
- Was the study described as double blind?	☐	☐	
- Was the method of blinding described and appropriate?	☐	☐	☐
3. **Withdrawals/dropouts**			
- Was there a description of withdrawals and dropouts? *(this should be rated as 'yes' if all participants are accounted for in the analysis and reasons for withdrawals are provided)*	☐	☐	☐

YES = 1
NO = 0
UNCLEAR = 0

SCORE: /5

Jadad, A.R., Moore, R.A., Carroll, D., Reynolds, D.J., et al (1996). Assessing the quality of reports of randomised clinical trials: is blinding necessary? Controlled Clinical Trials, 17, 1-12.

Controlled Trial Quality Assessment Form

Reviewer's Initials:
Authors:
Pub Year:

	Y	N	U
1. Is the sample representative of the population from which it is drawn?	☐	☐	☐
2. Were the controls drawn from a similar population to the study sample?	☐	☐	☐
3. Were the controls comparable to the study sample on all confounding factors?	☐	☐	☐
4. Is the inclusion/ exclusion criteria clearly stated?	☐	☐	☐
Randomisation			
5. Was the trial described as randomised?	☐	☐	☐
6. Was the method of randomisation adequate? *(adequate e.g. random numbers table, computer generated, coin toss etc.; inadequate e.g. alternation, case record number, DOB etc.)*	☐	☐	☐
Allocation concealment			
7. Was allocation concealment adequate? *adequate e.g. central allocation at trial office, coded containers from pharmacist or other method where the trialist could not be aware of treatment; inadequate e.g. alternation, ward admission, DOB or other information already known by trialist)*	☐	☐	☐
Blinding			
8. Was the trial described as double blind?	☐	☐	☐
9. Was the treatment allocation masked from the participants and the outcome assessor?	☐	☐	☐
10. Was the treatment allocation masked from the investigators?	☐	☐	☐
Outcomes			
11. Were the relevant outcomes measured in a standard, valid and reliable way?	☐	☐	☐
Follow-up			
12. Was the follow-up long enough for outcomes to occur? *(if follow-up is ≥6 months score 'yes'; if <6 months score 'no')*	☐	☐	☐
Completeness			
13. Were the drop out rates for each condition stated with	☐	☐	☐

explanations given? *(if none lost to follow-up then score 'yes')*

14. Was an intention-to-treat analysis performed? ☐ ☐ ☐

YES (Y) = 1
NO (N) = 0
UNCLEAR (U) = 0

Score: /14

Case Series Quality Assessment Form

Reviewer's Initials:
Authors:
Pub Year:

	Y	N	U
1. Were the data collected prospectively?	☐	☐	☐
2. Is the sample representative of the population from which it is drawn?	☐	☐	☐
3. Did the study include at least 30 participants?	☐	☐	☐
4. Did all the participants enter the study at a similar point in their disorder progression?	☐	☐	☐
5. Are the inclusion/ exclusion criteria explicitly stated?	☐	☐	☐
6. Was the follow-up long enough for outcomes to occur? *(if follow-up is ≥ 6 months score 'yes', if < 6 months score 'no')*	☐	☐	☐
7. Were the relevant outcomes measured in a standard, valid and reliable way?	☐	☐	☐
8. Are the results of the study clearly described?	☐	☐	☐
9. Were the data adequately analysed using appropriate statistics?	☐	☐	☐

YES = 1
NO = 0
UNCLEAR = 0

SCORE: