NCCHTA

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RESEARCH PROTOCOL: NOT FOR DISTRIBUTION

1. PROJECT TITLE:

01/07/02: Neuroleptics in Adults with Aggressive Challenging Behaviour and Intellectual Disability

ACRONYM: NACHBID

LEAD APPLICANT: Professor Peter Tyrer, Head of Department of Psychological Medicine, Division of Neuroscience and Psychological Medicine, Faculty of Medicine, Imperial College London, St. Mary's Campus, Room 402, 4th Floor, Paterson Centre, 20 South Wharf Road, London W2 1PD.
Tel. No./Ext.: 020 7886 1648 & 1996
Fax No.: 020 7886 1995

CO-APPLICANTS:
1. Professor Declan G.M. Murphy, Maudsley Centre for Behavioural Disorders, Institute of Psychiatry.
2. Professor Martin Knapp, Centre for Economics of Mental Health, Institute of Psychiatry.
3. Professor Nick Bouras, Mental Health in Learning Disability, Kings College, South London and Maudsley NHS Trust.
4. Dr. Zed Ahmed, Department of Psychological Medicine, Welsh Centre for Learning Disabilities (WCLD).
5. Prof. Shoumi Deb, Department of Psychiatry, The University of Birmingham, Queen Elizabeth Psychiatric Hospital.
6. Dr. Sherva Cooray, Kingsbury Community Hospital, Brent Primary Care Trust.
7. Dr. Mike Crawford, Department of Psychological Medicine, Faculty of Medicine, Imperial College of Science Technology and Medicine.

2. PLANNED INVESTIGATION

Research Objectives

1) To carry out a three-arm parallel design randomized controlled trial of a typical neuroleptic drug haloperidol, an atypical neuroleptic drug, risperidone, and placebo in non-psychotic patients presenting with aggressive challenging behaviour among those under treatment from learning disability services.
2) To compare short and long-term outcomes in terms of reduction in aggressive challenging behaviour (primary outcome), improved quality of life, reduction in burden of carers, and cost of care (secondary outcomes), in the three arms of the trial and to assess any adverse effects of the three interventions.

Existing Research

Several investigators have shown high lifetime prevalence rates for general behavioural and psychiatric disorders in people with learning disabilities [7]. These rates vary widely, from 20%-64%, and are dependent upon the setting and diagnostic criteria used. The rates also seem to increase with the severity of learning disability (LD). This matter is complicated by the fact that the diagnosis of a specific psychiatric disorder becomes more difficult as the severity of learning disability increases [7].

The currently favoured definition of 'challenging behaviour' is 'any culturally abnormal behaviour(s) of such intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behaviour which is likely to seriously limit use, or result in the person being denied access to, ordinary community facilities' [13]. Challenging behaviour must be viewed in a social context: a particular behaviour could be seen as challenging in one situation, but appropriate in another situation. The social context of challenging behaviour is vital to its understanding and treatment, and should be considered when comparing epidemiological research on the subject [7].

Antipsychotic drugs were first introduced into psychiatric practice in the 1950s, and were shown unequivocally to be effective in the treatment of schizophrenia ten years' later [8]. Bair and Herold [3] published the first report of the use of chlorpromazine in the treatment of people with learning disability and challenging behaviour and since then the use of these drugs has become extremely common. Antipsychotic drugs are prescribed regularly for people with learning disability, with 22 – 45% of learning disabled clients in hospital and about 20% of LD clients in the community receiving antipsychotic medication[17,9,6]. However, the prevalence of psychiatric illness in learning disabled clients is only 8-15%. These prevalence figures indicate that the use of antipsychotic medication is very high in people with learning disabilities, despite the fact that the proportion suffering from a mental illness is relatively small. The vast majority of antipsychotic medication is used for management of behavioural problems. As it has been estimated that up to 12% of people with learning disability in community settings and up to 37% of those in hospitals exhibit challenging behaviour, [9,16] the public health importance of this subject is very clear. With the relocation of this population into the community with only a few beds in specialist units, the use of these drugs is now spread over a larger number of settings. In many of these the only regular medical input is from general practitioners and supervision from skilled staff is often lacking, so if antipsychotic drugs are to be used in treating challenging behaviour we need clear evidence of their efficacy and handicaps in such settings.

Whilst there have been previous studies of the use of antipsychotic medication in people with both LD and challenging behaviour they have been unsatisfactory with regard to the establishment of efficacy and ability to generalize to most of the settings in which antipsychotic drugs are given. A recent systematic review of antipsychotic medication in the treatment of people with both challenging behaviour and LD found eight randomized controlled trials of antipsychotic drugs versus placebo medication but concluded that these 'provided no evidence of whether antipsychotic medication helps or harms adults with learning disability and challenging behaviour [7]. Our proposed study aims to remedy this deficiency in a large multicentre pragmatic trial in both hospital and community settings.

Although early studies were all carried out with typical antipsychotic drugs e.g haloperidol, these drugs have a high incidence of extrapyramidal side effects, including acute dystonias, which makes their use in acute settings risky. Not surprisingly, there has been a gradual switch to the newer atypical drugs whose common feature is a much lower incidence of these side effects. The general use of the atypical drugs is now recommended by the Department of Health[11]. Risperidone is one of the commonly prescribed ayptical antipsychotics that is of established efficacy[22] and it is frequently used in the treatment of people with learning disability. Risperidone, in conjunction with behavioural interventions, was used to reduce aggression and assault, self-injury, and property destruction in 33 institutionalised adults with LD in a study by Lott et al.[19], and this showed that risperidone was well tolerated in this population. Risperidone is a potent antipsychotic that has been tested in a cross-over study by Van den Borre et al.[29] in six different learning disability centres in the treatment of behavioural disturbances in people with LD. The study suggested that risperidone was superior to placebo in reducing symptoms but however more studies are needed.

In the present state of knowledge, we judge that a multicentre parallel design study comparing haloperidol, risperidone and placebo, in which a pragmatic design is followed and in which cost-effectiveness is a major component, is the best way of evaluating the value of antispychotic drugs in the treatment of aggressive challenging behaviour. As aggression to self or others in learning disability is estimated to cost the NHS and Social Services a minimum of £50-140 million per annum [21], even a small reduction achieved would carry great savings, quite irrespective of improvements in morbidity and quality of life and a reduction of stress to staff.

Research Methods

Hypotheses to be tested:
Three NHS regions (London, South Wales and Birmingham) are needed for a multicentre randomised controlled trial to recruit sufficient patients to test the null hypotheses that:
1) Compared to placebo antipsychotic drugs do not reduce the incidence of aggressive behaviour in those with learning disability and challenging behaviour.
2) There is no difference between the cost-effectiveness of prescribing risperidone, haloperidol or placebo in those with aggressive challenging behaviour.

Study Design:
A three-arm parallel design trial of placebo, haloperidol and risperidone is selected as the most appropriate to answer the research question. We will include patients who have not taken antipsychotic drugs by depot injection in the past three months or oral antipsychotic drugs in the past week but may have received it in the past. Those who are taking other oral antipsychotic drugs may also be included provided they satisfy the criteria for inclusion (below) and provided that there is a washout period at the time of inclusion in the trial with no antipsychotic drug treatment taken for at least one week.

If patients with epilepsy were excluded as many as 30% of those otherwise eligible would not have treatment available. The risks of epilepsy with risperidone are not sufficiently great to exclude patients. It is our intention to carry out baseline ECG, blood pressure, pulse and haematological investigations in those patients with pre-existing cardiovascular disease.

An external radomisation officer based at a different site in London from either of the main centres will randomise patients after receipt of baseline data is confirmed, using a block

randomisation code prepared for each centre. After baseline assessment patients will be allocated to risperidone, haloperidol or placebo, treated initially with 1mg of risperidone/2.5mg of haloperidol or placebo daily, with increase if necessary up to 2 mg of risperidone/5 mg of haloperidol daily by 4 weeks, and maintenance therapy for 8 further weeks. Assessments will occur at baseline, four and twelve weeks, and follow-up at six months. As some prescribing physicians start treatment with doses of ¼ or ½ tablet (i.e 0.5-1mg risperidone and 1.25-2.5mg haloperidol this will be permitted with an increased dose planned later. Doses greater than 2mg of Risperidone/5mg of haloperidol should only be used in exceptional cases i.e. where there has been no change in symptoms OR in a case of a symptomatic deterioration AND no clinically important adverse events (e.g. EPS, sedation). All patients will have the option to continue the anti-psychotic drugs for six months if necessary. All patients have the option of treatment as usual including other therapeutic and psychological treatments during this period with the exception of any other antipsychotic drugs. The study treatment will not be freely available to the patients after the six-month period of their trial participation, and the patient will have to obtain the drug if necessary through their relevant NHS prescription procedure.

Setting:
Learning disabled people in community settings, supported housing and NHS residential facilities, with the setting stratified at randomisation.

Target population:
All referrals to community services in the study areas with mild, moderate or severe learning disability showing aggressive challenging behaviour in the absence of a mental state diagnosis of a psychotic disorder. The study will recruit patients in a total of four centres which include separate sites; **Centre 1 – London North of Thames**, includes sites Brent, Ealing, Harrow, Hammersmith & Fulham, Havering, Hounslow, Kensington & Chelsea, Barnet, Enfield, Redbridge and Waltham Forest; **Centre 2 – South London**, includes Lambeth, Lewisham and Southwark; **Centre 3 – Wales and South West England** includes Cardiff, South Wales and SW England; **Centre 4 – Birmingham** includes South Birmingham, Warwickshire, Hereford and Worcestershire, Dudley, Walsall, Sandwell, North Birmingham, Shropshire, West Birmingham, North Staffordshire, South East Staffordshire and Mid Staffordshire; Centre 5 – Leicester; Centrer 6 – Brisbane Queensland (Austrailia); Centre 7 – North England, including Gateshead and Cumbtia; Centre; Centre 8 - East Midlands, includes Nottingham and Lincoln; Centre 9 – Cambridgeshire and Norfolk. Centre 1, 2, 7, 8 and 9 are supported by the United Kingdom mental health research Network (UKMHRN)..

Cost measurement:
We will collect comprehensive data on all health, social care, housing and other services used by individuals included in the study using a tailored version of the Client Service Receipt Inventory. Services will be costed as long-run marginal opportunity costs (LRMC) using national figures [21.] For services where national figures are not available or not suitable we will calculate best estimates of LRMC values from locally collected expenditure figures. We will also collect data on time inputs of care by family and other unpaid carers, and the impacts on carers in terms of limitations on employment. Costs of informal care will also be included in the analyses. Sensitivity analyses will explore *inter alia*, the consequences of adopting different values for the costs of informal care.

Planned Interventions

Antipsychotic (neuroleptic) drugs in the form of haloperidol and risperidone, a widely used atypical antipsychotic drug against placebo intervention for twelve weeks initially and six months if necessary. The local clinical team will decide on a threshold for use of rescue medication and the use of rescue medication will be noted and the primary measure score taken at that time. Rescue medication in the form of lorazepam, (1-4 mg within BNF limits) daily will be left to the clinician's discretion. A detailed record of medication given will be recorded and if lorazepam is given daily for more than 2 weeks at any one time it will be withdrawn in tapered doses over 4 days. It is not expected that this will be used for more than one in three of the patients and then only occasionally. The option of taking additional medication may reduce the effect size of haloperidol-risperidone-placebo differences but will aid compliance and is consistent with the pragmatic design of replicating ordinary practice. We expect a likely rate of loss to follow-up of no more than 20 percent.

Planned Inclusion/Exclusion Criteria

Inclusion criteria

1. Clients with learning disability with an IQ level of less than 75.

2. Aged between 18-65 years

3. Clients with challenging behaviour and aggression (defined by at least two episodes of aggressive behaviour with a total Modified Overt Aggression Scale (MOAS) score of at least 4 in the past 7 days). Each will give informed consent based on information that is understandable to each learning disabled individual. Carers will be approached for those who are unable to give informed consent. Consent will be given in writing and witnessed.

Exclusion criteria

1. Clients who have taken, depot neuroleptics/injected antipsychotic medication treatment within the last three months or continuous oral antipsychotic medication within the last week. *Please note clients taking an oral antipsychotic occasionally, as and when necessary (i.e. PRN) can be included in the study, if medication has not been taken in the past week.*

2. Clients with a clinical diagnosis of schizophrenia or another psychotic disorder.

3. Clients under mental health legislation will be excluded from the study.

4. Clients who have participated in any therapeutic or non-therapeutic research study during the last three months.

Ethical Issues

In the absence of a robust evidence base, psychiatrists confront the dilemma of prescribing psychotropic medication for persons with learning disability and challenging behaviour as a therapeutic trial or deprive a vulnerable group of a potentially beneficial intervention. The

latter strategy is unethical and possibly negligent, contrary to human rights within the context of equity and social inclusion. It is thus our aim to recruit as many learning disabled individuals as possible including those with moderate to severe learning disability whether by informed consent or assent otherwise they will be disenfranchised.

Where possible, informed consent will be obtained from all suitable clients. It has been agreed that the local practitioners will raise the purpose and the ethical issues about this research with local interested groups such as self-advocacy groups, parents groups, and care managers. The intention is to obtain general agreement from the local community involved with learning disability services that such research is necessary and that consent in writing can be given by those individuals who have the capacity to consent.

Where the patient is able to communicate and understand sufficiently well to gain proper informed consent and decide for himself or herself, the patient will be asked to give their consent in writing. Where possible, informed consent will be obtained based on information that is understandable to each learning disabled individual. Where the patient is not legally competent to make a treatment choice, they will be treated in their 'best interests', which will be defined in a manner appropriate to clinical research. This will include certain safeguards: 1) The agreement of relatives/and or advocates will be sought. The advocate/relative may be able to provide assent on behalf of their client/relative. 2) A professional worker should not be asked to act as a proxy relative in this study. 3) The assent of the relative/primary carer should be obtained in all cases, even where the patient has given consent. 4) Any objection by a relative or primary carer will be noted. 5) Where an adult patient who lacks capacity for consent indicates for whatever reason that they are unwilling to participate in the study, they should not be included in the study, even if there is agreement/assent from the relatives/advocate or primary carer. We believe that these requirements adequately reflect the position in English Law regarding therapeutic research and the ethical position reflected in the MRC Ethics Series research section 7.2.1-7.2.4 on p17-18 in the MRC Ethics Series[20]. A copy of this document will be provided for each research centre or site participating in the study.

All participating patients will be given a NACHBID study card and this card will be carried at all times and presented at every medical consultation during their six month study period.

The Chair of the Parent's Forum of the Westminster Society for Carers' of People with Learning Disability is giving advice to the study team and is a member of the Steering Group for the trial. However, we are expecting further aspects to be raised by local ethics committees, clinicians and carers during the implementation phase of the study and are ready to make adjustments to the consent process to take account of these issues.

Proposed Sample Size

We have carried out a pilot study to help in determining an appropriate sample to get adequate power to test the main hypothesis. In order to calculate the sample required for the trial pilot data on symptoms and behavior were collected at five centres. The Aberrant Behavior Checklist[2] was completed for 55 subjects who met the eligibility criteria for the study. Those data were used to estimate baseline ABC scores in the proposed trial. Scores on the ABC were normally distributed with a mean of 35 and a standard deviation of 22.8. We believe that a difference of 12 points on the ABC between those receiving risperidone or haloperidol and placebo would be clinically significant. This is also the difference that was observed between

learning disability patients with behavioral disturbance treated with risperidone and placebo in a small double-blind placebo-controlled cross-over trial conducted by Van den Borre and colleagues [29]. A sample size of 194 subjects (97 taking risperidone and 97 placebo) would be required to have 90% power to detect a difference of this magnitude at 5% level of significance[1]. Comparison of haloperidol and placebo would utilise data from the same 97 subjects taking placebo and a further 97 subjects taking haloperidol. We therefore need to obtain data on 291 subjects. With a potential drop out rate of 20%, a total sample of 363 is required. We will therefore recruit 363 subjects to the study (121 to receive risperidone, 121 haloperidol and 121 placebo).

Statistical Analysis

A record will be kept of those clients who are excluded or who dropout from the study due to their need for treatment. These background and other outcome data will be used in the final cost analysis. Analysis will be done utilising SPSS and STATA software. Baseline data on challenging behaviour and other routine data will be used to ascertain whether study groups differed. Our primary outcome will be aggressive challenging behaviour (measured by MOAS*)*. Differences in scores on the MOAS will be compared among those receiving risperidone, haloperidol and placebo using univariate tests (t-test and Mann-Whitney test). The primary analysis will be carried out on an intention-to-treat basis, thus intention-to-treat analysis will be used. A regression analysis will then be conducted in order to take account of any differences in baseline MOAS scores and a correction for baseline MOAS and other potential confounding factors will be done. Differences in quality of life will then be examined using the same statistical techniques. The primary statistical analysis will be analysis of co-variance between baseline and six months with adjustment made for baseline differences, with repeated measures analysis of variance for variables that we test on the two assessment occasions.

The main economic evaluation will be a cost-effectiveness analysis from the societal perspective, comparing changes in the primary outcome (reduction in aggressive challenging behaviour) and total costs (services and carer inputs) between risperidone, haloperidol and placebo patients. This will be supplemented by a cost-consequences analysis (examining total and component costs alongside all outcomes). The latter is of course less deterministic than the computed incremental ratio of a cost-effectiveness analysis, but will provide potentially helpful additional information. Health and social care and public sector perspectives can also be explored in order to inform associated policy discussions.

Proposed Outcome Measures

Outcome measures in research on challenging behaviour should not be confined to the frequency, duration and intensity of the target behaviours, but on equally meaningful outcomes, which take the social context into account[7]. For this study we have chosen aggressive behaviour as our primary outcome. The main reason was that serious challenging behaviour is usually aggressive in presentation and anti-psychotic drugs are prescribed for this reason. Although aggressive behaviour is selected as the primary outcome, we also wish to include as secondary outcomes changes in quality of life, reduction in burden of carers, aberrant behaviour scores and global improvement.

The Aberrant Behaviour Checklist (ABC) was a scale developed to assess drug and other treatment effects on people with severe learning disability. The scale has been found to have wide generality irrespective of institutional setting and rater source[2]. This scale measures challenging behaviour but it is debatable as to whether it measures accurately the aggressive component of challenging behaviour.

The Overt Aggression Scale (OAS) was developed by Silver & Yudofsky [27] for the accurate documentation of aggressive episodes when they occur and to assess the effectiveness of interventions in the treatment of violent patients. The utilisation of the OAS assures that significantly more aggressive episodes and behaviours will be documented. The use of the OAS has particular value in documenting and assessing individual patterns of aggression, such as verbal or physical aggression, week-to-week fluctuations in aggressive behaviours, patterns of aggression among patient groups, types of interventions utilised to control aggressive behaviours e.g. antipsychotic medication and the effects of pharmacological and psychosocial intervention [27,30].

Sorgi et al. [28] based on good experience using the Nurse's Observation Scale for Inpatient Evaluation (NOSIE), a retrospective instrument that records ward behaviour, modified the Overt Aggression Scale by reformatting the 16 classes of types of aggressive behaviour into 16 scale items. This new scale included the frequency of occurrence of the 16 items rated on a 5 point Likert scale. This modified instrument had ease of administration and therefore the potential to be a useful measure of both aggressive incidents and aggressiveness in a psychiatric inpatient population [28,15]. Ratey and Gutheil, [25] reflecting on the use of the Overt Aggression Scale and the Modified Overt Aggression Scale, found that the practicality of standardised observational techniques remains an OAS issue but that the MOAS is most effective as a frequency counter, but in autistic samples, the level and intensity of aggression is such that frequency alone is not the best tool for measurement. For this study we will utilise the Modified Overt Agression Scale (MOAS) as the primary outcome measure because it has demonstrated good reliability, and has previously been used in a learning disabled population with good face validity. However, psychometric properties have been only been tested in psychiatric population and we intend to test these properties from the results of this study. The Aberrant Behaviour Checklist (ABC) – Community Version will be for use as a secondary outcome because as an assessment it is widely used and has good psychometric properties which have been tested in learning disabled population. Both assessments will enable a broad-based assessment to be made of improvement in aggressive challenging behaviour (ACB).

1. Multi-axial Classification

Clinical assessments, using the multi-axial classification DSM-IV format with ICD10 codes [10] at baseline will involve:

1. Interview with carer
2. Interview with client (where possible)
3. Meeting with other relevant staff
4. Review of case notes

2. Mini PAS-ADD

For psychiatric symptoms, the Mini PAS-ADD [23] will be completed by interview with a key informant at baseline only. To increase reliability, this schedule uses a glossary of symptom definitions to guide the coding. The instrument has been designed so that the information collected can aid the subsequent process of diagnosis by a psychiatrist or psychologist.

The schedule produces scores relating to the following psychiatric disorders: Each category has an accompanying threshold score.

a. Depressive Disorder
b. Anxiety Disorder
c. Hypomania/Mania or Expansive mood
d. Obsessive Compulsive disorder
e. Psychosis
f. Dementia or Unspecified Disorder
g. Autistic Spectrum

3. Modified Overt Aggression Scale (MOAS)

Primary outcomes measure for clients with aggressive challenging behaviour (ACB) and learning disability. This assessment will be scored weekly from baseline to the end of the patient's six month intervention period.

4. Aberrant Behaviour Checklist (ABC) - Community

Secondary outcome measure for clients with aggressive challenging behaviour (ACB) and learning disability. To be administered at baseline, 4 weeks, 12 weeks and six months follow-up.

5. Client Service Receipt Inventory [CSRI][4]

Costs will be calculated from data collected by the Client Service Receipt Inventory (CSRI) tailored to the service context [5]. A key informant for each sample member will complete CSRIs. The CSRI will be retrospective for six months and will be assessed at baseline and at six months follow-up for this study.

6. Clinical Global Impressions Scale [CGI]

The CGI scale measures the severity of mental illness and global improvement, with the severity of illness recorded at baseline and both severity and global improvement will be recorded at 4 weeks, 12 weeks and 6 months follow-up [14].

7. Uplift/Burden Scale

The study will utilise the Uplift and Burden Scale [24] for the measurement of burden of care of carers (Carer's Scale). This 23-item scale has 6 uplift items and 17 burden items and is the preferred measure because it is suitable for short-term interventions. To be assessed with the primary carer at baseline, 4 weeks, 12 weeks and 6 months follow-up.

8. Quality of Life Questionnaire [QOL-Q]

The quality of life of people with learning disability and mental health problems and/or challenging behaviour, will be measured by the 40-item Quality of Life Questionnaire (QOL-Q) [26]. To be assessed with the patient at baseline, 4 weeks, 12 weeks and 6 months follow-up.

9. The UKU Side Effect Scale [18]

Extra-pyramidal side effects will be recorded using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale at baseline, 4 weeks, 12 weeks and 6 months follow-up.

10. Additional Interventions Checklist

At the request of the funding organisation the NCCHTA, we have constructed an additional interventions checklist to measure other non-drug treatment interventions received by the patient during the study intervention period. Records of other interventions will be kept from four weeks before baseline and for the 6-month intervention period.

Independent Supervision of Trial

An independent data monitoring and ethics committee will be established to monitor (a) recruitment of patients to the trial, (b) ethical issues of consent, (c) quality of data (including missing data) and (d) any other factors that might compromise the progress and satisfactory completion of the trial. This will include an independent statistician, Dr. Tony Johnson of the MRC Biostatistics Unit, Cambridge, Dr. Deborah Rutter, ethics committee member, Ms. Bharti Rao and Mrs. Ula Nur, trial Statisticians and Prof. Peter Tyrer. There will also be an external steering committee established, which includes Prof. Peter Tyrer and Prof. Declan Murphy as trial working group representatives, Prof. William Fraser, Prof. Sheila Hollins, Dr. Angela Hassiotis and Dr. Stephen Tyrer for the monitoring of the clinical aspects of the study.

Study Procedures

Clients will be assessed using the multi-axial classification DSM-IV format with ICD10 codes and identification of diagnostic assessment based on the mini PAS-ADD assessment.

Clients with a clinical diagnosis of a psychotic disorder will be excluded from the study. An independent statistician from the MRC complex interventions collaborative group, using a permuted blocks technique, will perform randomisation and be the data guardian.

Summary of steps:

1. A key informant will be identified for each new referral
2. Clinical assessment of client (Multiaxial Assessment)
3. Independent assessment of psychiatric and behavioural symptoms (Mini PAS-ADD) for those that Step 2 identified the presence of a psychiatric disorder.
4. Consent of the client and assent/agreement of the carer will be sought.
5. Independent Assessor completes the baseline MOAS, ABC-Community, UKU Side Effect Scale with key informant, CSRI, CGI (illness only), Uplift Burden Scale, QOL and additional Interventions checklist.
6. Random allocation to either haloperidol, risperidone or placebo arm of trial for each client.
7. Commencement of treatment - treated initially with 1mg of risperidone/2.5mg of haloperidol/placebo daily, with increase if necessary up to 2 mg risperidone and 5 mg haloperidol daily by 4 weeks, and maintenance therapy for 8 further weeks and if necessary for six months. Doses greater than 2mg of Risperidone/5mg of haloperidol should only be used in exceptional cases i.e. where there has been no change in symptoms OR in a case of a symptomatic deterioration AND no clinically important adverse events (e.g. EPS, sedation).
8. Follow-ups: 4 weeks, 12 weeks and 6 months
   Independent reassessment of psychiatric and MOAS (weekly), ABC-Community, UKU Side Effect Rating Scale, CSRI (6 months only) and CGI with key informant, Uplift Burden Scale with primary carer, QOL (patient), and additional interventions checklist.

3. TIMETABLE AND MILESTONES

May - Sept. 2001 (prior to full proposal) – Pilot Study for Power Calculations (Done)
Oct 2001- June 2002 - MREC and submission and piloting of procedures.
Start Date – 01/07/02

July – September 2002 – LREC submission and preparation of study recruitment procedures, drug packaging and assessments for baseline and follow-up.
November 2002 – October 2004 - piloting of recruitment procedures and recruitment of patients at a total of four centres which include separate sites; **Centre 1 – London North of Thames**, includes sites Brent, Ealing, Harrow, Hammersmith & Fulham, Havering, Hounslow, Kensington & Chelsea, Barnet, Enfield, Redbridge and Waltham Forest; **Centre 2 – South London**, includes Lambeth, Lewisham and Southwark; **Centre 3 – Wales and South West England** includes Cardiff, South Wales and SW England; **Centre 4 – Birmingham** includes South Birmingham, Warwickshire, Hereford and Worcestershire, Dudley, Walsall, Sandwell, North Birmingham, Shropshire, West Birmingham, North Staffordshire, South East Staffordshire and Mid Staffordshire. The recruitment rate of a minimum of 3 patients per centre per month or minimum of 3 patients per researcher per month.
April 2005 - completion of trial follow-up
End of Funding - 30/06/05
Dec 2004 – Dec 2005 data analysis, cost effectiveness evaluation, writing reports and papers.

4. EXPERTISE

1) The project would be linked to an MRC Collaborative Group under Professors Peter Tyrer and Michael King, which is evaluating all aspects of complex interventions in primary and secondary mental health care. This project is of particular interest to the Group because of its ethical aspects and difficulties in selecting simple dichotomous outcomes.

2) This project intends to review the ethical issues in detail. Potential obstacles such as obtaining informed consent, especially for moderate to severe LD clients, the use of medication to control behaviour thus creating an increase in the prescription of anti-psychotic medication to the study population, in addition to possible side effects will be considered.

3) An advisory group will be appointed to aid the consortium in the ethical and recruitment aspects of the trial. This will involve both users and carers in learning disability and will pay particular attention to consent procedures and advocacy to support participants. We will emphasise improved QOL to the users and they will be involved with the full proposal. Users and carers will be part of the consortium.

5. JUSTIFICATION OF SUPPORT REQUIRED

The trial co-ordinator will co-ordinate project meetings, administer the project and supervise three full-time and one part-time research assistant employed to collect data and also serve as a back-up for data collection, cleaning and editing. This means that five researchers will be collecting data from over 300 patients across a large geographical area and this justifies the number of assistants, travel costs and need for a laptop computer. Each research assistant will be responsible for data collection for all measurements within their area. They will be responsible for ensuring that full data are collected, following the procedures set out by the scientific leads, and reporting their progress to the administrative co-ordination centre.

It will be necessary for the applicants and co-ordinators at each centre to meet regularly and also to liase with carer and user advisors, the data monitoring and ethics committee and for the results of the study to be disseminated. Although we recognise that the latter might be considered to be outside the scope of the grant we feel that the dissemination aspect is of particular importance in this subject.

Estimated excess costs are for the provision of haloperidol, risperidone and placebo tablets. There are no additional costs in health service care imposed by the study. Janssen-Cilag will pay Imperial College for the excess costs of dispensing medication and for the packaging down of the study tablets by the main study pharmacy at St. Mary's Hospital, Paddington. Imperial College will pay the participating pharmacies for their dispensing costs for the trial.

Pharmacy Procedures

This a double blind randomised controlled trial of haloperidol versus risperidone versus placebo. The research worker and clinicians must be blind to the medication taken by the patient. An identification/randomisation number will be allocated to patients for their trial duration. Three bottles of medication will be allocated to each patient. Each bottle containing the drug to which the patient has been randomised will be labelled with the patient's corresponding identification number. Three bottles should be sufficient for the duration of each patient's treatment. The first bottle contains 28 tablets for the first 4 weeks, the second contains 56 tablets for the next 8 weeks and the third contains 98 tablets for the next 14 weeks. Some of the patients will have the trial medication for 12 weeks only.

1. To dispense the drug for each new patient entering the study, the Research Associate (RA) needs to complete a "NACHBID Trial DISPENSING & RETURNS LOG". The form will then be given to the pharmacist and will be kept in the pharmacy. A further copy will be retained by the RA for her records. The pharmacist will supply the RA with the first bottle.

    - In the case that the patient enters in the trial, the RA will fax or bring back a copy of the "NACHBID Trial Prescription Form" signed by the Consultant Psychiatrist as soon as possible.
    - In the case that the patient finally doesn't enter in the Trial, the RA will bring back the bottle and the "NACHBID Trial Dispensing & Returns Log" will be destroyed. The bottle will then be dispensed to the next patient.

2. In some cases the RA could ask the Pharmacist to provide a patient prescription sheet from the Hospital for patients living in-group homes (e.g. Birmingham).

3. If at any time a patient needs more than a tablet per day in their prescription then the clinician/psychiatrist should tell the RA as soon as possible so that extra tablets can be made available for patients in such exceptional cases.

4. The Randomisation Unit of the Trial will post copies of the randomisation form to the trial pharmacists to keep them informed about patient details, randomisation group and the follow-up dates for each patient for planning the 8 week and 14 week bottles for each patient.

5. At 4 weeks and 12 weeks, the medication will be dispensed after the RA has completed the patient "NACHBID Trial Dispensing & Returns Log" form kept in the pharmacy. A copy will again be retained by the RA. The RA will fax or bring back a copy of the "NACHBID Trial Prescription Form" signed by the Consultant Psychiatrist as soon as possible.

6. The "NACHBID Trial Dispensing & Returns Log" needs to be completed and the tablet bottles returned (even if empty) to the pharmacy after each follow up. The original form will be kept in the pharmacy during the whole trial but the RA will be given a copy at each stage for her records.

7. The returned bottles should be kept in the pharmacy even when empty.

8. These procedures are applicable to all participating centre pharmacies for the trial. However, where there is agreement between the researcher and the pharmacist there can be flexibility in relation to the timing of delivery and storage of originals/copies of the 'NACHBID Trial Dispensing and Returns Log', the 'NACHBID Trial Prescription Form' and the returned bottles for each particular study centre.

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