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Augmentation of antipsychotic medication with anticonvulsant in the management of treatment resistant schizophrenia

Submission date
04/12/2020

Recruitment status
Stopped

Registration date
16/02/2021

Overall study status
Stopped

Last Edited
26/10/2023

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Schizophrenia is a severe mental illness that affects 1 in 100 people. The main treatment is with first-line antipsychotic drugs. However, for 1 in 3 patients, these drugs are ineffective at improving their symptoms.

In people whose illness is treatment resistant, the only alternative licensed medication is called clozapine. However, clozapine's use is restricted because of safety concerns and requires careful physical health monitoring and frequent blood tests. This leaves many patients with no treatment option.

We aim to investigate a potential treatment for these patients. This is a drug called valproate and is not licensed for this purpose. A survey across UK NHS trusts found that in nearly 20% of patients it is used in this way, costing ~£60 million per year to the NHS. There is some evidence to support this practice, but the evidence is inconclusive. Thus, whilst adding valproate to antipsychotic treatment is widely used, it is unknown if it helps reduce symptoms, improves quality of life or is cost-effective. Therefore, we aim to conduct a study that will answer these questions.

Who can participate?
Patients aged 18 and above of either gender who are not frail and have a diagnosis of schizophrenia or schizoaffective disorder with residual psychotic symptoms on their first-line antipsychotic will be recruited.

What does the study involve?
Participants will be assigned to either a placebo (inactive substance) plus antipsychotic or valproate plus antipsychotic arm. This is a multi-centre UK trial in which the medication phase is for one year. The efficacy of this combination will be assessed using psychiatric assessments and the cost-effectiveness will be assessed using service use by patients over a period of one year. They will also be followed for long-term outcomes for up to four years from the start of the trial.

What are the possible benefits and risks of participating?
Benefits:
Our screening and continued monitoring as part of the study will check if subjects are in good physical health. We will also ask questions about how they are feeling. All this means we can see any changes in their health and deal with them as soon as possible. Some people find this reassuring. If we find a medical problem, we will advise them and may refer them to their GP, care co-ordinator or psychiatrist.
If they take part, they will also be helping medical research. At the end of the study, they have to discontinue the study medication. As the study medication is available in the UK and can be prescribed by their doctor, if they feel they have benefited and wish to continue taking this medication, they can ask their doctor to start sodium valproate.
Risks:
Sodium valproate is a licenced drug in the UK that is used to treat a number of conditions including migraine and epilepsy. Like all medicines, sodium valproate can cause side effects, although not everybody gets them. Usually they are not serious and settle over a few weeks and stop after stopping sodium valproate.
Possible side effects of sodium valproate include
• tummy upset or nausea
• fine hand tremor
• change in liver enzymes and/or blood counts,
• hair loss or growth,
• weight gain,
• skin reactions,
• longer time for blood to clot when you have a cut and/or
• menstrual problems in women
Subjects could feel drowsy, especially if they are also taking other medications, and hence care should be taken if they drive, operate machines or do other things that require alertness. Also, alcohol intake is not recommended when on treatment with sodium valproate.
As with any medicine, very rarely people can have allergic or other serious reactions. Since the study medication can affect unborn children, subjects must not take the study medication if they are pregnant or plan to become pregnant.
The tablets include the following other ingredients commonly used to make them: cellulose, silica, gelatine (animal source; origin not known), emulsifier, talc, copolymer, triacetin, colouring, macrogol and lactose. Subjects could be allergic to these ingredients

Where is the study run from?
Kings College London (UK)

When is the study starting and how long is it expected to run for?
September 2019 to December 2025

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Sridhar Natesan, sridhar.natesan@kcl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Sridhar Natesan

ORCID ID
https://orcid.org/0000-0001-7499-1714

Contact details
Inst. of Psychiatry, Psychology and Neuroscience,
King's College London
Denmark Hill
London
United Kingdom
SE5 8AF
+44 (0)207 848 0013
sridhar.natesan@kcl.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2020-000420-19

Integrated Research Application System (IRAS)
275431

Central Portfolio Management System (CPMS)
47411

Study information

Scientific Title
AnTiconvuLsant AugmeNtation Trial In Schizophrenia: a randomised, pragmatic double-blind, placebo-controlled trial to assess the effectiveness of valproate augmentation of antipsychotic treatment in patients with residual psychotic symptoms

Acronym
ATLANTIS

Study objectives
Valproate augmentation of antipsychotic treatment in patients with residual psychotic symptoms will be superior compared to placebo on the Positive and Negative Syndrome Scale (PANSS) positive subscale at 12 months.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/12/2020, North East – Tyne & Wear South (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8265; tyneandwearsouth.rec@hra.nhs.uk), ref: 20/NE/0247

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Schizophrenia

Interventions
Patients who have a diagnosis of psychotic disorder and having residual symptoms inspite of taking first-line antipsychotics will be recruited if they meet the conditions for participation.

They will be randomly allocated 1:1 to either placebo (inactive pill) + continuing antipsychotic treatment arm or valproate + continuing antipsychotic treatment arm to be treated for a year. The researchers as well as patients will be kept blind to the allocation. Comparing the study medication's effect with dummy pills is the most effective way to prove a treatment's effect in medicine.

This is a UK multi-site study and all patients who start the trial will be analysed even if they discontinue the study medication earlier than planned or if they switch to a second-line medication called clozapine. The duration of the trial is for 4.5 years including data analysis and publication of report.

The trial will include a titration phase for valproate, the study medication, lasting for approximately 2 weeks followed by a maintenance phase for the remaining 50 weeks of the study. At the end of the 52-week treatment period, subjects will be down titrated over 2 weeks.

Outcomes (mental health, well being as well as side effects) will be measured at baseline, 3, 6 and 12 months using standard rating scales and service use will be collected to evaluate cost effectiveness of the study medication. Meetings will be arranged at a site close to where patient's stay and medication will also be dispensed to them. Safety assessments will also be carried out during these visits and patients will be allowed to continue only if they meet a predetermined safety criteria.

After patients have finished the medication period phase, they will be followed up using electronic health records till the end of the trial (up to four years from the start of the trial).

As it is a pragmatic trial, clinicians will also be able to adjust the antipsychotic dose, change formulation, change antipsychotics or even add if needed. The addition or change of antipsychotic to clozapine (second-line medication) will however be considered as discontinuation of the study intervention and patients will be withdrawn from the study medication after down titrating their valproate medication treatment.

Valproate will be started at 500mg each day and titrated up to a suitable dose not exceeding 2500mg each day based on their body weight reflecting clinical practice. The placebo group will receive a matching placebo (dummy pill) titration. To ensure that the treatment is optimal for each patient, and to promote patients' staying in the trial, further dose increased and decreases

of valproate will also be allowed in both arms within the dose range mentioned above.
Side effects will be measured using a rating scale and this rating scale will determine the optimal dose for each patient based on their tolerance.

Statisticians have determined that a total of 290 participants will be required to prove the superiority of valproate over placebo and with an estimate of attrition of 20% for both the groups we will need to recruit a total of 362 participants.

We did consult a patient group to determine the best way to study the medication's effect and they did debate comparing valparoate with clozapine. However they pointed out that real need was for a treatment where clozapine wasn't suitable or acceptable and so a comparison against clozapine was not relevant. Hence this design of the clinical trial was finalized.

If patients consent, then we will also involve their caregivers as part of the study. They will be provided with information about the study and we will involve them in improving study compliance and some of them will be part of the service user and career group that will be set up at each site to advise us on implementation and feedback.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Psychotic (positive), negative and general symptom severity in schizophrenia measured using the Positive and Negative Syndrome Scale (PANSS) positive subscale at the 12-month visit

Key secondary outcome(s)
1. Psychotic (positive) symptom severity in schizophrenia measured using the PANSS positive score at 6 months
2. Psychotic (positive), negative and general symptom severity in schizophrenia measured using the PANSS at 3, 6 and 12 months
3. Psychotic (positive), negative and general symptom severity (PANSS) factor scores at baseline at 3, 6 and 12 months
4. Severity of the patient’s illness measured using the Clinical Global Impression scale (Schizophrenia version) at baseline, 3, 6 & 12-month follow-up visits
5. Aggression levels will be measured using the Modified Overt Aggression Scale at baseline, 3, 6 & 12-month follow-up visits
6. Depression will be measured using the Calgary depression scale for schizophrenia (CDSS) at baseline, 3, 6 & 12-month follow-up visits
7. Manic symptoms will be assessed using Young’s Mania rating scale (YMRS) will be measured at baseline, 3, 6 & 12-month follow-up visits
8. Patient reported outcomes will be evaluated using the Short Warwick-Edinburgh Well-being scale (SWEMWBS). It will be measured at baseline, 3, 6-month and 1-year time points
9. Cost effectiveness will be assessed using measures collected at baseline, 3, 6 & 12-month follow-up visits: the Client Service Receipt Inventory (CSRI), PANSS and the 36-item short form health survey (SF-36)
10. The discontinuation of the intervention will be measured at the 3, 6-month and 1-year time points. We will also record the cause of discontinuation under the following categories: (i) lack of efficacy, (ii) adverse effects, (iii) switch to clozapine, (v) lost to follow-up, (vi) contraindicated

with medication that has been added or (vii) personal reasons
11. We will evaluate on an annual basis the long-term symptomatic and functional outcomes beyond the 12-month period primarily using electronic notes to determine service use (admission/crisis/home treatment/other service use) and medical history including HoNOS (Health of the Nation Outcome Scales)to determine outcomes after patients have finished the trial. HoNOS is a global clinical outcomes tool that is routinely collected across all mental health services in the NHS and can be accessed electronically
12. Number starting clozapine treatment within the study trial period measured using patient records

Completion date
31/12/2025

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria
Current inclusion criteria as of 04/05/2021:

1. Aged 18 and above at the time of consent
2. Adequate command of English to understand the information leaflet
3. Capacity to consent to participation in the study
4. Confirmation of DSM-5 diagnosis of schizophrenia or schizoaffective disorder using SCID-5
5. PANSS total symptom severity score > 70
6. At least one PANSS psychotic item rating of at least moderate severity (> 3 on one or more psychotic item rating in PANSS)
7. Received treatment with at least one non-clozapine antipsychotic drug at adequate dose (as defined by Maudsley guidelines)for a duration of at least 6 weeks and in case of a depot be stable for at least 2 treatment cycles or at least 30 days
8. On a stable dose of antipsychotic treatment for at least 2 weeks in case of oral dosage forms
9. Good adherence to antipsychotic treatments as determined by a score > 4 on the Medication Adherence rating scale
10. Female subject of child bearing potential must agree to the MHRA pregnancy prevention programme which includes a negative serum pregnancy test, use of a highly effective form of birth control and signing an annual risk acknowledgement form

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Previous inclusion criteria:

1. Aged 18 and above at the time of consent
2. Adequate command of English to understand the information leaflet
3. Capacity to consent to participation in the study
4. Confirmation of DSM-5 diagnosis of schizophrenia or schizoaffective disorder using SCID-5
5. PANSS total symptom severity score > 70
6. At least one PANSS psychotic item rating of at least moderate severity (> 3 on one or more psychotic item rating in PANSS)
7. Received treatment with at least one non-clozapine antipsychotic drug at adequate dose (as defined by Maudsley guidelines)for a duration of at least 6 weeks and in case of a depot be

stable for at least 2 treatment cycles or at least 30 days
8. On a stable dose of antipsychotic treatment for at least 2 weeks in case of oral dosage forms
9. Good adherence to antipsychotic treatments as determined by a score > 4 (ideally > 6) on the Medication Adherence rating scale
10. Female subject of child bearing potential must agree to the MHRA pregnancy prevention programme which includes a negative serum pregnancy test, use of a highly effective form of birth control and signing an annual risk acknowledgement form

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Subject having a rating of 4 or above on the clinical frailty scale
2. Female subject who is pregnant or breast-feeding
3. Subject with a known history of urea cyclic disorder
4. Subject with a known history of porphyria
5. Subject with a known history of severe renal insufficiency
6. Subject with a known history of a mitochondrial disorder and in the opinion of the recruiting researcher will impair the safety of the subject and/or the scientific integrity of the study
7. Subject with carnitine palmitoyltransferase (CPT) type II deficiency
8. Subject currently taking clozapine
9. Subject currently taking valproate
10. Subject who had stopped taking valproate in the past six weeks prior to screening due to adverse effects
11. Any recent change (<2 weeks) change in antipsychotic regimen
12. Subject answers “yes” to “Suicide Ideation” Items 4 (active suicide ideation) with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSR during the screening visit
13. Subject has attempted suicide within 3 months prior to screening
14. Subject having known hypersensitivity to valproate or other ingredients in the tablet or placebo
15. Significant sustained abnormality when vital signs are measured at screening
16. Patients with a personal or family history of significant liver disease (e.g. severe hepatic dysfunction, cirrhosis)
17. Any other medical condition in the opinion of the recruiting researcher that will impair the safety of the subject and/or the scientific integrity of the study
18. Participation in a clinical trial within 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)
19. Participation in a research study that in the opinion of the investigator will affect the safety

of the volunteer or scientific integrity of either study
20. Taking a drug that may have a clinically significant effect on the metabolism of valproate or where valproate may have a clinically significant effect on its metabolism including oxcarbazepine, lamotrigine, phenobarbital, primidone, phenytoin, ethosuximide, rufinamide, phenytoin, carbapenem antibiotics, topiramate, acetazolamide, warfarin and other coumarin anticoagulants and in the opinion of the recruiting researcher will impair the safety of the subject and/or the scientific integrity of the study
(added 04/05/2021)
21. Women of childbearing potential unwilling to follow the study contraception requirements
22. Subject with a known history of active liver disease

Date of first enrolment
01/01/2021

Date of final enrolment
29/02/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
King's College London
19 Denmark Hill
London
United Kingdom
SE5 8AF

Study participating centre
Royal Edinburgh Hospital
The University of Edinburgh
Division of Psychiatry
Edinburgh
United Kingdom
EH10 5HF

Study participating centre
NHS Lothian
2 - 4 Waterloo Place
Edinburgh

United Kingdom
EH1 3EG

Study participating centre
The University of Manchester
Division of Psychology and Mental Health, School of Health Sciences
Oxford Rd
Manchester
United Kingdom
M13 9PL

Study participating centre
Prestwich Hospital
Greater Manchester Mental Health NHS Foundation Trust
Harrop House
Bury New Road
Prestwich
Manchester
United Kingdom
M25 3BL

Study participating centre
Fulbourn Hospital
Psychological Wellbeing Service
Cambridgeshire and Peterborough NHS Foundation Trust
Elizabeth House
Cambridge
United Kingdom
CB21 5EF

Study participating centre
West London Mental Health NHS Trust
1st Floor, Wing B
1 Armstrong Way
Southall
London
United Kingdom
UB2 4SD

Study participating centre

Maudsley Hospital
South London and Maudsley NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 8AZ

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR127755

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Protocol file	version v4	16/02/2021	04/05/2021	No	No