LAST-RD
Lithium And
Standard Therapy in
Resistant Depression

World Health Organisation Collaborative Centre
for Research and Training in Mental Health
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Lithium And Standard Therapy in Resistant Depression

RANDOMIZED EVALUATION OF THE EFFECTIVENESS OF LITHIUM IN SUBJECTS WITH TREATMENT-RESISTANT DEPRESSION AND SUICIDE RISK.

AN INDEPENDENT, PRAGMATIC, MULTICENTRE, PARALLEL-GROUP, SUPERIORITY TRIAL.

Protocol 5.1 March 2009

STUDY OVERVIEW

Title:	Randomized evaluation of the effectiveness of lithium in subjects with treatment-resistant depression and suicide risk. An independent, pragmatic, multicentre, parallel-group, superiority trial.
Protocol Author:	LAST Investigators
Department:	World Health Organisation Collaborative Centre (WHOCC) for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy
Principal Investigators	Corrado Barbui, Andrea Cipriani, Michele Tansella (WHOCC University of Verona)
Trial Manager:	Michela Nosè (WHOCC University of Verona)
Staff:	Marianna Purgato, Francesca Girlanda (WHOCC University of Verona)
Trial statistician:	Giulia Bisoffi (Head, Statistical Office, Azienda Ospedaliera di Verona)
IND/Non-IND:	Independent Study
Total Number of Study Centers:	About 60-80
Country:	Italy
Number of Subjects:	230
Setting:	Italian community mental health services. Inpatients and outpatients.
Length of follow-up	12 months
Timelines:	Enrolment: 2010-2011; follow-up: 2012
Population:	Patients with treatment resistant depression and suicide risk
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BACKGROUND

Some people with depression do not respond well to initial treatment [1]. International guidelines define treatment-resistant depression (TRD) as that which fails to respond to two or more antidepressants given sequentially at an adequate dose for an adequate time [2,3]. It has been estimated that under ordinary circumstances up to 30-40% of patients with unipolar depression fail to make a satisfactory improvement, and 10-15% of these may develop chronic depression [4]. In clinical practice, treatment guidelines usually recommend switching to an antidepressant belonging to a different pharmacological class [5], combination strategies (two antidepressants simultaneously prescribed) or augmentation strategies (antidepressant plus lithium or atypical antipsychotics or thyroid hormone or lamotrigine or pindolol) [2].

In TRD, self-harm and suicide ideas represent alarming psychopathological symptoms [1]. These may lead to self-harm and suicide attempts and, in up to 10% of cases, to completed suicides. While it is difficult to examine the effects of treatments on rates of completed suicide, intervention following non-fatal suicidal behaviour is more amenable to evaluation. This is directly relevant to suicide prevention, because the risk of suicide following deliberate self-harm (DSH) is considerable. Thus, at least 1% of patients referred to general hospitals in the United Kingdom for DSH die by suicide within a year of an episode of DSH, and 3-5% within 5-10 years [6]. Rates of suicide following DSH are considerably higher in some other countries where the DSH population has an older age profile and includes more patients with major psychiatric disorders [7]. Looked at the other way around, 40-50% of people who die by suicide have previous episodes of DSH [8,9]

In this difficult-to-treat patient population data on therapeutic interventions following non-fatal suicidal behaviour are very scant. Hawton and colleagues, who carried out a Cochrane review of clinical trials that evaluated the effect of specific treatments for DSH patients, found only three antidepressant trials [10,11]. The summary odds ratio indicated only a non-significant trend towards reduced repetition of deliberate self-harm for antidepressant therapy compared with placebo (0.83; 0.47 to 1.48). In addition to antidepressants, very recently the beneficial effect of lithium in

terms of suicidal behaviour has been highlighted by Cipriani and colleagues [12], who conducted a systematic review and meta-analysis of randomized trials to investigate the effect of lithium, compared to placebo and other active treatments, on the risk of suicide, deliberate self-harm, and all-cause mortality in patients with mood disorder. The meta-analysis of 32 trials found that lithium was more effective than placebo. However, the included trials were not primarily designed to measure this outcome measure, and heterogeneous patient populations were enrolled, including unipolar and bipolar patients. Additionally, while some trials included acutely depressed patients, euthymic cases were enrolled in other studies. Another meta-analysis, which included studies conducted in patients with unipolar depression, suggested that lithium has an antisuicidal effects in recurrent major depressive disorder, similar in magnitude to that found in bipolar disorders [13]. However, a major limitation of this analysis is that non-randomised studies were pooled together with randomised trials [13].

Very recently, the results of the SUPLI trial were published. The SUPLI-Study is the first prospective, randomized, double blind, placebo-controlled multi-centre trial focusing on the proposed suicide preventive effects of lithium in patients with suicidal behaviour. Patients with a recent history of a suicide attempt were treated with lithium versus placebo during a 12 month period [14]. A total of 167 patients were included in the analysis, of whom around 75% had a diagnosis of major depression, 20% of adjustment disorder, and 5% were suffering from dysthymia or related depressive disorders [15]. Survival analysis showed no significant difference of suicidal acts between lithium and placebo-treated individuals (adjusted hazard ratio 0.517; 95% CI 0.18-1.43). However, post hoc analysis revealed that all completed suicides had occurred in the placebo group accounting for a significant difference in incidence rates (P = 0.049). On the basis of these figures authors concluded that lithium treatment might be effective in reducing the risk of completed suicide in adult patients with affective disorders.

On the basis of the evidence base collected so far, lithium may therefore be protective against suicidal behaviour, but currently no randomised trial has been performed to primarily test this hypothesis in patients with TRD.

STUDY CLINICAL QUESTION

The primary aim of the LAST study is to assess whether lithium is effective in reducing the risk of suicidal behaviour in subjects with treatment-resistant depression and suicide risk. Secondary aims of the study are: (a) to assess whether lithium is effective in improving depressive symptomatology in subjects with treatment-resistant depression and suicide risk; (b) to assess the tolerability profile of lithium.

STUDY DESIGN

LAST is a prospective, multicentre, randomized, parallel-group, superiority trial that will follow patients over a period of 12 months. Patients with treatment-resistant depression (TRD) and risk of suicide will be randomly assigned to (i) lithium plus usual pharmacological and non-pharmacological treatment or to (ii) usual pharmacological and non-pharmacological treatment. Patients and clinicians will not be blind to pharmacological treatments provided during the trial. In order to limit the potential bias introduced by lack of blindness, an independent adjudicating committee, blind to treatment allocation, will validate the events that will constitute the primary outcome. Patients will be assessed at baseline before randomization and then every month after random allocation until the completion of the 12-month follow-up. All phases of the trial will be recorded following the CONSORT statement [16,17].

ELIGIBILITY CRITERIA

Inclusion criteria:

(a) Diagnosis of major depression (clinical diagnosis, guided by DSM-IV criteria).
(b) History of attempted suicide or deliberate self-harm in the previous 12 months.
(c) Inadequate response to at least two antidepressants given sequentially at an adequate dose for an adequate time for the current depressive episode.
(d) Uncertainty about which treatment arm would be best for the participant.
(e) Age 18 or above.

(f) Agreement between investigator and patient to enter the study.

Exclusion criteria:

(a) In addition to major depression, a primary diagnosis of any concurrent Axis I disorder (according to DSM-IV criteria) will constitute an exclusion criterion; by contrast, any concurrent Axis II disorder (according to DSM-IV criteria) will not constitute an exclusion criterion.

(b) Previous exposure to lithium was associated with lack of efficacy or unwanted adverse reactions.

(c) Clinical conditions contraindicate the experimental treatment arm (for example thyroid or kidney disease or abnormalities).

(d) Pregnant/lactating women.

(e) Women of childbearing potential not practicing a reliable method of contraception.

PRIMARY OUTCOME DEFINITION

Suicide completion and acts of deliberate self harm (DSH) will constitute the composite primary outcome. The term "suicide" is defined as an act with a fatal outcome, deliberately initiated and performed by the person with the knowledge or expectation of its fatal outcome.

DSH is defined as intentional self-poisoning or self-injury, irrespective of motivation [18,19]. Self-poisoning includes the intentional self-ingestion of more than the prescribed amount of any drug, whether or not there is evidence that the act was intended to result in death. This also includes poisoning with non-ingestible substances and gas, overdoses of "recreational drugs" and severe alcohol intoxication where clinical staff consider such cases to be an act of intentional self-harm (rather than recreational binge drinking). Self-injury is defined as any injury that has been intentionally self-inflicted, including self-cutting. The intention to end life may be absent or present to a variable degree. Other terms used to describe this phenomenon

are "attempted suicide" and "parasuicide" [19]. Some acts of DSH are characterised by high suicidal intent, meticulous planning (including precautions against being found out), and severe lethality of the method used. Other acts of DSH are characterised by no or low intention of suicide, lack of planning and concealing of the act, and low lethality of the method used.

INDEPENDENT ADJUDICATING COMMITTEE

An independent adjudicating committee, blind to treatment allocation, will review all deaths and all hazardous acts reported during the 12 months of follow-up by the treating clinicians. The committee will have the role of identifying, among deaths, the cases of suicide, and among hazardous acts those that constitute acts of DSH. Only the cases of suicide and those of DSH validated by the committee will constitute the primary outcome.

PARTICIPANTS

Patients will be recruited in Italy. Community psychiatric services agreeing to take part to the study will be asked to recruit consecutive patients meeting the inclusion/exclusion criteria over a 24 month period. Patients meeting the criteria for random allocation will be randomly allocated to lithium plus usual pharmacological and non-pharmacological treatment or to usual pharmacological and non-pharmacological treatment and followed for 12 months. A total number of 60-80 psychiatric services will be involved.

Baseline assessment

Before entering the study, patients will be asked to provide informed consent to participate. Clinical and demographic characteristics will be collected at baseline using a Recruitment Form (RF). The RF will include sociodemographic and clinical information, diagnostic information according to the Mini Neuropsychiatry Interview

(MINI) [20], severity of illness information according to the Quick Inventory Depression Scale (QIDS) [21], a self-rated instruments that has been shown to have good psychometric properties [22]. Information will be gathered on previous DSH acts. Information on laboratory and electrocardiography (ECG) parameters will be collected according to local usual care. The RF will be administered by the treating clinician before random allocation (see Study schedule).

Follow-up assessments

Follow-up data will be obtained each month after random allocation using an electronic Follow-Up Form (e-FUF). The e-FUF will collect information on deaths and DSH. At month 3 and month 6, the e-FUF will collect the following additional information: lithium oral dose, lithium plasma level, concomitant drug treatments, QIDS scores, adverse events (see Study schedule). At the end of the 12-month follow-up period, information will be collected using a Follow-Up Form (FUF). The FUF will collect information on deaths and DSH, lithium oral dose, lithium plasma level and concomitant drug treatments, QUIDS scores, adverse events. Additionally, the FUF will include a check list for the diagnosis of major depression (MINI criteria) (see Study schedule). At each follow-up assessment, information on laboratory and electrocardiography (ECG) parameters will be collected according to local usual care.

PHARMACOLOGICAL TREATMENTS

Lithium is currently marketed in Italy for the treatment of major depression. Lithium will be prescribed according to Italian usual care.

Patients allocated to lithium will be administered an oral starting dose ranging between 150 and 300 milligrams. Suggested final oral dose will have to achieve plasma levels of 0.4 to 1.0 mmol/L. Clinicians will be free of increasing or decreasing the dose according to clinical status and circumstances. Dose changes will be recorded. Following randomization, treatment is to be taken daily for 1 year unless some clear

reason to stop develops. Patients allocated to the lithium arm will receive usual pharmacological and non-pharmacological treatment as clinically indicated. Any other pharmacological treatment will be allowed.

Patients allocated to the control arm will receive usual pharmacological and non-pharmacological treatment as clinically indicated. Patients allocated to the control arm will not be allowed to receive lithium. Any other pharmacological treatment will be allowed.

Routine care outside the trial continues as usual. During the study, participants will be seen as often as clinically indicated with no extra visits required for the trial.

RANDOM ALLOCATION PROCEDURE

Patients will be randomly assigned to one of the two treatment groups with an equal probability of assignment to each treatment (allocation ratio 1:1). A centralised randomization procedure will be employed. The trial biostatistician will prepare the sequence of treatments randomly permuted in blocks of unequal size. The randomization schedule will be generated using nQuery Advisor, release 7.0. Recruiting physicians will contact an administrator at the World Health Organisation Collaborative Centre for Research and Training in Mental Health and Service Evaluation of the University of Verona who will access a computerised system that will provide, after information on the enrolled participant is entered and inclusion criteria are verified, the patient's identification number (ID) and the allocated treatment.

PRIMARY OUTCOME

(1) Suicide completion and acts of DSH during the 12 months of follow-up will constitute the composite primary outcome.

SECONDARY OUTCOMES

(1) All-cause mortality during the 12 months of follow-up.
(2) Suicide mortality during the 12 months of follow-up.
(3) Acts of DSH during the 12 months of follow-up.
(4) Change in severity of depressive symptoms from baseline to 12 months.
(5) Adverse reactions during the study.

POWER ANALYSIS FOR SAMPLE SIZE CALCULATION

On the basis of the data extrapolated from three antidepressant clinical trials that employed completed and attempted suicide as the primary endpoint, it is expected an event rate of around 25% within 12 months (primary study endpoint) [10,11]. It is hypothesised that the augmentation with lithium (experimental group) will show a clinically significant advantage by producing an event rate of 10%. A sample size of 210 patients (105 in each group), achieves 80% power for a 0.05 level of two-sided log-rank test for equality of survival curves to detect the hypothesized difference in survival at 12 months (31 events expected). Assuming that 10% of the participants could be lost within 12 months, or could not provide valid data, 230 patients will be enrolled.

STATISTICAL ANALYSIS

The statistical analysis will be masked, i.e. the trial biostatistician will be blinded to the treatment groups until the analysis has been completed. Moreover, the trial biostatistician will not be involved in determining patients' eligibility, in administering the treatment, in measuring the outcomes or in entering data. All analyses will be performed using Stata/SE, Release 10.1.

General approach

Data lock will occur at 12 months, when data will be available for all participants. The pattern of missing values will be explored and interactions between treatment group and non-completers/completers will be examined with respect to demographic variables and baseline disease assessment.

The Intention to Treat (ITT) population will consist of all subject randomly assigned to the competitive treatment strategies. This ITT population will be used for the analysis of the primary outcome and for the analyses of the secondary outcomes.

Patients with missing values and patients lost during follow-up will contribute to the analysis of the primary and secondary outcomes only for the time during which data are available (censoring). Missing values in depressive symptom ratings will be imputed using the Last Observation Carried forward (LOCF) approach: depressive ratings will be carried forward from the last available assessment to the 12-month follow-up assessment.

Additionally, patients in the lithium arm that will discontinue lithium during follow-up will be analysed, at 12 months, according to the initial randomised treatment group (lithium arm). Similarly, patients in the usual care arm that will start lithium during follow-up will be analysed, at 12 months, according to the initial randomised treatment group (usual care arm). This approach will be applied to the analysis of the primary outcome and to the analyses of all 5 secondary outcomes.

In order to check the consistency of this ITT approach, the primary outcome will then be analysed using a per-protocol (PP) approach. According to the PP approach, patients in the lithium arm that will discontinue lithium during follow-up will contribute to the analysis of the primary outcome only for the time between random allocation and lithium discontinuation (censoring). Similarly, patients in the usual care arm that will start lithium during follow-up will contribute to the analysis of the primary outcome

only for the time between random allocation and the beginning of lithium treatment (censoring). The analysis of the PP population will be used for confirmatory purposes only. If less than 5% of patients switch from the allocated treatment to the competitive treatment, the PP analysis will not be performed.

Only the events adjudicated by the Independent Adjudicating Committee (IAC, see below) will be considered for the analysis of the primary outcome.

ANALYSIS OF THE PRIMARY OUTCOME

Kaplan-Meier estimates for the time from randomized treatment assignment until the first event that constitutes the primary outcome will be plotted to compare the treatment's effect, and log-rank test will be performed to test for differences.

A Cox proportional hazard model will be used to explore the effect of possible confounding or interaction factors (secondary analysis). Gender and age will be included into the model regardless of statistical significance criteria. The proportional hazard assumption of the effects will be tested.

ANALYSIS OF THE SECONDARY OUTCOMES

Time from randomized treatment assignment until all-cause mortality during the 12 months of follow-up will be analysed through a log-rank test for difference in survival between the two groups. The same method will be applied for the following secondary outcomes: suicide mortality, deliberate self-harm. Multivariate analyses will be performed to explore the possible role of prognostic factors on outcomes.

Change in severity of depressive symptoms from baseline to 12 months will be analysed as a continuous variable and as a dichotomous variables, where individuals showing an improvement of al least 50% will be considered treatment responders. Change in severity of illness at 12-months will be compared between the two groups of

treatment through appropriate statistical methods for repeated measurements (paired t-test or McNemar non parametric test according to the variables distribution). The proportion of patients with the occurrence of the dichotomous outcome of interest (treatment response) will be compared between the two groups of treatment through the chi-square test (or the Fisher's exact test when appropriate). When possible, a multivariate analysis will be performed through a Poisson regression model with a robust error variance.

The proportion of patients with adverse reactions during the study will be compared between the two groups of treatment through the chi-square test (or the Fisher's exact test when appropriate).

INTERIM ANALYSES

No interim analysis is planned for this trial.

ETHICAL ASPECTS

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the Declaration of Helsinki and in keeping with local regulations.

LAST investigators will ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The coordinating centre will maintain a list of sub-investigators and other appropriately qualified persons involved in the study.

Before being enrolled in LAST, subjects will consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to them. An informed consent document that includes both information

about the study and the consent form will be given to participants. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document will be in a language understandable to the participants and will specify who informed the subject. The person who informs the subject will be a physician. After reading the informed consent document, the subject, or his/her legal representative, must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussion.

According to the ICH E6 Guideline for Good Clinical Practice, subjects who will be enrolled in the trial with the consent of the subjects' legally acceptable representative will be informed about the trial to the extent compatible with the subjects' understanding and, if capable, the subject will be asked to sign and personally date the written informed consent.

DATA MANAGEMENT

All study data will be entered in a computerised database and stored by the World Health Organisation Collaborative Centre for Research and Training in Mental Health and Service Evaluation of the University of Verona. The person entering the data will not be involved in determining patients' eligibility, administering treatment, or determining outcome. The correctness and consistency of the data will be ensured by the double-entry technique and by a set of electronic and manual edit checks. The consistency of the data between the recruitment and follow-up forms and the computerised database will be verified. Masked data will be transferred to the Statistical Office of the Azienda Ospedaliera di Verona for statistical analysis.

In accordance with the Declaration of Helsinki, the patients' confidentiality will be preserved at all times and the contents of the recruitment and follow-up forms will not be disclosed to any third party. The data collected in the study corresponding to a

patient will be recorded anonymously. Patients will be identified by a number, their initials and date of birth, both in the recruitment and follow-up forms and in the database. Total confidentiality of data is guaranteed, especially the identity of the participants.

TRIAL MANAGEMENT

Trial Steering Committee (TSC)

The Trial Steering Committee will monitor and supervise the progress of LAST toward its objectives. The TSC will review relevant information from other sources and will consider the recommendations from the Event Adjudication Committee and from the External Safety and Efficacy Committee.

Independent Adjudicating Committee (IAC)

The Independent Adjudicating Committee will be constituted by three clinical psychiatrists who are independent from the LAST investigators. The IAC will be blinded to the treatment groups. The IAC will review each month all suicide-related events reported in the e-FUF and will validate and adjudicate the events that will constitute the primary outcome.

External safety and efficacy committee (ESEC)

The external safety and efficacy committee will be independent of the trial and will ensure that LAST remains ethical and safe. The committee will convene six months after the beginning of the enrolment phase, and on a regular basis thereafter. Unblinded safety and efficacy data will be evaluated by the committee. The committee will be provided with masked safety and efficacy summaries by the trial biostatistician of the Statistical Office of the Azienda Ospedaliera di Verona, and with the corresponding codes by the data manager of the World Health Organisation

Collaborative Centre for Research and Training in Mental Health and Service Evaluation of the University of Verona. The committee will suggest modifications of the protocol to enhance subject safety and will recommend early termination of the study if there is strong evidence that lithium poses a safety concern to subjects. Throughout the trial, the ESEC will have the possibility to directly access all source data/documents for trial-related monitoring and inspections. Role and responsibilities of the committee will follow the DAMOCLES charter for clinical trial data monitoring committees [23].

Standard Operating Procedures

Standard Operating Procedures (SOPs) describing all phases of the study will be developed following a predefined template, consecutively numbered and disseminated. Throughout the whole duration of the study, hard copies and electronic versions of all study documents will be stored in dedicated archives.

Trial monitoring

LAST investigators will ensure that the trial is adequately monitored. The purpose of trial monitoring will be to verify that the reported data are accurate, complete, and verifiable from source documents. Recruiting centres will allow the coordinating centre, at its discretion, to monitor and audit the conduct of any procedure related to the study. This includes the right to inspect any facility being used for the study and to examine any relevant procedures and records.

Data ownership

All study data belong to the LAST investigators.

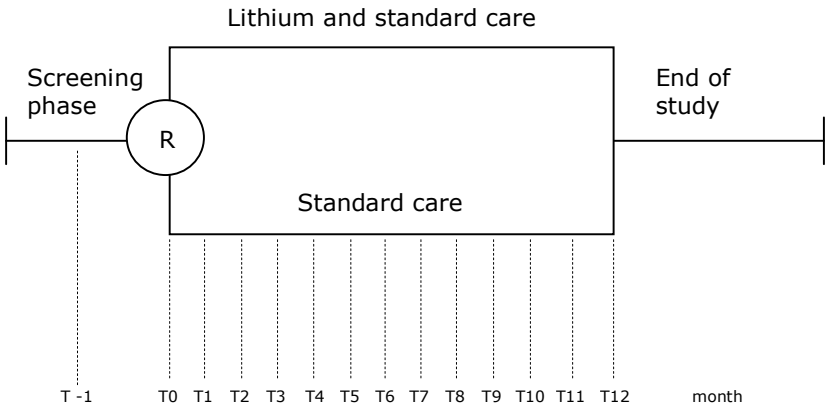
Publications

The primary publication from LAST will be attributed to the LAST Investigators. The names of all investigators who randomize patients within the trial will be listed with the Principal Investigators and Steering Group at the end of the primary publication. Subsequent publications will be approved by the TSC in agreement with the Publication Protocol.

Funding

LAST has been approved, and is financially supported, by the Agenzia Italiana del Farmaco (AIFA), Cod.: FARM77Z3BL.

STUDY FLOW-CHART



STUDY SCHEDULE

	T -1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Informed consent signed	X													
Review of eligibility criteria	X													
Recruitment form (RF)		X												
MINI		X												X
QUIDS		X			X			X						X
Patient number assigned		X												
Random allocation		X												
electronic-FUF			X	X	X	X	X	X	X	X	X	X	X	
Follow-up Form (FUF)														X
Adverse events reporting		← Any time according to Italian legislation →												

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