Sertraline versus placebo in patients with major depressive disorder and undergoing haemodialysis (ASSertID): a randomised, controlled feasibility trial.

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Abstract

BACKGROUND AND OBJECTIVES:
Depression is common in patients on haemodialysis (HD) but data on the benefits and risks of antidepressants in this setting are limited. We conducted a multicentre randomised double-blind placebo-controlled trial of sertraline over 6 months in HD patients with depression to determine study feasibility, safety and effectiveness.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS
HD patients in five UK renal centres completed the Beck Depression Inventory II (BDI-II). Those scoring ≥ 16, and not already on treatment for depression were invited to undergo diagnostic interview to confirm major depressive disorder (MDD). Eligible patients with MDD were randomised to receive the study medication – either sertraline or placebo. Outcomes included recruitment and drop-out rates, change in the Montgomery-Åsberg Depression Rating Scale (MADRS) and BDI-II, and qualitative information to guide design of a large scale trial.

RESULTS
709 patients were screened and enrolled between April 2013 and October 2014. 231(32.6%) had BDI-II ≥16, 58 (25%) of whom were already receiving treatment for depression; 63 underwent diagnostic interview; 37 were diagnosed with MDD; 30 were randomised. 21 completed the trial, 8/15 on sertraline and 13/15 on placebo (p=0.046). Dropouts due to adverse and serious adverse events were greater in the sertraline group. All occurred in the first 3 months. Over 6 months depression scores improved in both groups. BDI-II score fell from 29.1 ± 8.4 to 17.3 ± 12.4 (p<0.001) and MADRS score from 24.5 ± 4.1 to 10.3 ± 5.8 (p<0.001). There were no differences between sertraline and placebo groups.

CONCLUSIONS
Though small, this is the largest randomised trial to date of antidepressant medication in HD patients. Our results highlight recruitment issues. No benefit was observed, but trial size and the substantial dropout render consideration of benefit inconclusive. A definitive trial could employ shorter follow-up and include depressed patients already taking antidepressants.

Trial registered, ISRCTN06146268.

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Introduction

The prevalence of adult patients receiving renal replacement therapy (RRT) continues to increase across the developed world. In 2012 the numbers on dialysis ranged from 133 per million population in South Africa to 2903 in Taiwan[1]. Dialysis patients have a high morbidity and mortality. Patients' experience of living with dialysis is significantly affected by many factors including physical symptoms, substantial comorbidity - particularly cardiovascular, complex dialysis regimens, high pill burdens and the need for dietary and fluid restrictions [2-4].

Though common in this setting depression is difficult to diagnose, not least because of the symptom overlap between depression and advanced kidney disease [5-7]. Estimates of prevalence of depression in dialysis patients vary between 39% based on screening and 23% based on psychiatric interview [8]. Depression in this is associated with reduced quality of life, increased prevalence of cardiovascular disease, and increased mortality. It may lead to reduced treatment adherence, reduced self-care behaviour, and subsequently greater healthcare resource use [9-11]. The prevailing view is that depression is often not recognised, so only a small proportion of patients receive treatment [12-15]. There is little research on treatment options for depression in dialysis patients, particularly use of antidepressant medication [12]. A 2009 Cochrane review identified only one small Randomised Controlled Trial (RCT), with 14 patients. Results were inconclusive [16;17]. It is perhaps unsurprising that recent systematic reviews recommended a large well-designed RCT in this setting [8;18].

NICE (National Institute for Health and Care Excellence) guidance for depression in adults with chronic physical health problem recommends a stepped care approach to treatment, including prescribing medication for people with persistent mild to moderate depression [19]. Sertraline, a selective serotonin reuptake inhibitor, has been found to be effective and to have fewer side effects than many other commonly prescribed anti-depressants, except for diarrhoea [20]. Several studies found sertraline to be safe for patients with cardiovascular disease [21;22].

Given the lack of proven efficacy of antidepressants in this setting and the increased risk of adverse drug events due to severely impaired renal function and the high pill burden, we carried out this study. The primary aim was to assess the feasibility of undertaking a large RCT to evaluate the acceptability and effectiveness of sertraline to treat depression in patients on haemodialysis (HD). Efficacy and safety outcomes were also evaluated.

Methods

Study Design

We conducted a multicentre double-blind, parallel group, placebo controlled, feasibility randomised trial of sertraline in HD patients with mild to moderate MDD. Ethics approval was received (National Research Ethics Service Committee London - Bentham, reference 12/LO/1554). The study took place in five Renal Units in the Midlands and South-East of England and involved screening and trial phases. The study design is fully described in the published protocol [23]. The trial is registered, ISRCTN06146268, and was carried out in concordance with Declaration of Helsinki.

Screening phase

Patients over the age of 18 years who had been receiving treatment by HD for 3 months or more were approached. Patients who could not read and speak English were excluded. Consenting patients completed the Beck Depression Inventory (BDI-II)[24] questionnaire. Data relating to demographics, medical and psychiatric history, and dialysis treatment were also collected. Those with a BDI-II score ≥ 16, not on treatment for depression (antidepressants or psychological therapies) currently or in the past 3 months and without any pre-defined exclusion criteria, which included planned living-donor kidney transplant within the period of the trial, a prognosis of less than a year, several associated medical conditions and contraindicated medications (Table 1), were approached to undergo diagnostic interview by a psychiatrist using the Mini International Neuropsychiatric Interview (MINI)[25] to confirm the presence of Major Depressive Disorder (MDD). Following this, consenting patients diagnosed with mild-moderate MDD and with a score of 18 or above on the Montgomery-Asberg Depression Scale (MADRS)[26] were randomised into the Trial Phase. Patients with severe depression or suicidal ideation were excluded and referred urgently to psychiatric services. Patients were also excluded who had evidence of cognitive impairment on the Folstein Mini mental status exam using a cutpoint of 23 [27]. We sought written informed consent from patients at three separate points in the study, before screening, before diagnostic interview and before randomisation to enter the trial

Trial Phase

Randomisation and masking

After confirmation of MDD, the study psychiatrist used a web-based randomisation programme (Norwich Clinical Trials Unit (CTU)) to assign patients to receive either sertraline hydrochloride or placebo. Block randomisation with stratification for each centre was used. The placebo was microcrystalline cellulose and magnesium stearate. Sertraline

and placebo tablets were identically encapsulated (Royal Free Hospital Drug Manufacturing Unit). The patients, dispensing pharmacies, study psychiatrist, research nurses, all clinicians, trial manager and study statistician were blind to the allocation of the study medication. The CTU data manager and the manufacturing pharmacy held the randomisation list.

Procedures

Following randomisation patients were prescribed the study drug at an initial dose of 50 mg daily. Patients were reassessed by the psychiatrist at 2 weeks, and at 2, 4 and 6 months and assessed monthly by the research nurse. MADRS was repeated at 2, 4 and 6 months and BDI-II at 6 months. There was an option for the psychiatrist to increase the dose of study drug to a maximum of 100 mg at 2 and 4 months if deemed indicated. Routine biochemical and haematological data were collected monthly, along with information on adverse and serious adverse events. Plasma samples for pre- and post-dialysis sertraline levels were obtained at the 4 or 5th follow-up appointment. Semi-structured interviews were carried out in a sub-group of 16 patients to explore their experience of taking part in the trial.

Outcomes

We assessed both feasibility and clinical outcome measures, listed in the published protocol [23]. The primary feasibility outcome was the number of patients, emerging from the screening phase, who entered and completed the RCT. Secondary outcomes included the number of patients not meeting the eligibility criteria, the number who refused to take part in the trial, the number who withdrew from the trial and the reasons given and the number and nature of adverse events reported. Changes in MADRS and BDI-II over the course of the study were also evaluated. To estimate medication adherence we also analysed information on the number of returned tablets and pre-and post-dialysis sertraline levels.

Statistical analysis

As a feasibility study, sample size was determined by the need to estimate the population variance of the outcome measures, and pragmatic considerations about potential recruitment. A sample size of 30 per arm (N=60) was selected allowing the population variance to be estimated with reasonable precision (1.2 x variance). Previous studies suggested that 30% of patients would screen positive on the BDI-II, 50% of patients scoring ≥16 on the BDI-II would be subsequently diagnosed with MDD, and 50% would agree to be randomised. Given a target of 60 patients representing 7.5% of the screen sample, the target for screening was 800 patients.

To explore the feasibility of the study, the analysis focused on the conversion of patients from screening to randomisation, protocol and drug adherence, and the patients' experience of participating in the trial. Analysis was also planned to evaluate both the observed variance in the clinical outcome measures (MADRS, BDI-II) to allow estimation of the effect size, and the observed gain in the outcome given treatment by sertraline versus placebo accepting limitations in study power. We also evaluated the number of adverse events. With regard to efficacy, all available patient data were included in estimated parameters. Baseline characteristics of the patients dropping-out and completing were compared. Most reporting was descriptive but where comparisons are reported a t-test was used (between groups, or repeated as appropriate). Analyses were carried out using STATA version 13.1 (StataCorp LP). An independent data monitoring committee, consisting of a statistician, nephrologist and a lay person, oversaw the study. They met twice during the study.

Results

The study took place over 25 months between April 2013 and May 2015. The CONSORT flow diagram for the study is shown in Figure 1. We approached 1353 patients to enter the screening phase. Two hundred and forty-three were excluded mainly due to inability to read and understand English. Of the remaining 1110 patients, 709 (64%) consented and underwent screening. On screening, 231 patients (32.6%) had a BDI-II (24) score of 16 or above. Of these 39 (16.9%) were not considered for the trial phase because of current anti-depressant medication, 12 (5.2%) because of current psychological therapy and 17 (7.4 %) both. Other reasons for ineligibility were medical and other psychiatric problems 34 (14.7%) and contraindicated medications 17 (7.4%)(Table 1). Thirty-eight patients (16.5%) declined to consent.

Sixty-three of those eligible for the trial phase, consented to be seen by the study psychiatrist for diagnostic interview. Thirty-seven of these (58.7%) were diagnosed with major depressive disorder (MDD). However three had recently started anti-depressants, one had severe cardiac disease, one severe cognitive impairment, one was diagnosed with substance misuse, and another preferred to be seen by their primary care physician. Thirty consented to enter the RCT. On unblinding it was apparent that 15 had been randomised to each group.

Baseline characteristics were similar in the sertraline and placebo groups. The sample were predominately men (77%). The sertraline group was on average 5 years older. For the

whole study sample, mean age was 59.0±13.8; 60% were white, 20% Asian, 20% other ethnicities. Fifty percent were married or living in a civil partnership and 33% lived alone. Over 80% had at least one co-morbidity, with diabetes and heart disease the most common. Thirty three percent had a history of depression and 17% had previously used anti-depressants (Table 2).

Twenty one patients completed the trial (70%), eight (53%) in the sertraline group and 13 (87%) in the placebo group ~~($\chi 2=3.97$;~~ (p=0.046). In the sertraline group, there were six dropouts within the first 2 months. One patient died following cardiac arrest having taken one tablet. Three patients withdrew because of adverse events (one after 3 days with nausea, another after 12 days with headaches and dizziness and the third due to insomnia after 23 days). The fifth withdrew, concerned about side-effects, having taken no study medication. The sixth patient was admitted for a prolonged hospital stay with leg ulcers shortly after randomisation and was subsequently withdrawn without having taken any study medication. At 3 months a seventh patient withdrew because of sweating and palpitations. In the placebo group, one patient withdrew after the baseline interview concerned about taking additional medication and a second decided against continuing after three months. The number of dropouts due to adverse or severe adverse events was greater in the sertraline group (33% v 0%: p=0.042). Patients who withdrew were older (70 vs 54 years, p=0.001) and had lower baseline haemoglobin levels (109 vs 121 g/L, p=0.04).

With regard to clinical outcomes, there was a significant fall in the BDI-II from baseline to month 6 (29.1 ± 8.4 to 17.3 ± 12.4: p<0.001) and in the MADRS scores (24.9 ± 4.3 to 10.7 ±5.2: p<0.001) with similar significant falls in both sertraline and placebo groups (Figure 2). Mean change in MADRS score over the six months of the study was -14.5 (CI -20.2 to -8.8) in the sertraline group and – 14.9 (CI -18.4 to -11.5) in the placebo group. Changes in BDI II were similar at -15.7 (CI -24.3 to -7.1) in the sertraline group and –13.0 (CI -19.6 to -6.4) in those on placebo. There were no statistically reliable differences between the groups. ~~For the BDI-II, half the patients had fallen below the cut-off for depression at 6 months.~~ For the MADRS score there were no differences between groups at any other time-point with respect to change from baseline values. The maximum difference occurred at 2 months, at which stage 9 patients remained on sertraline and 14 on placebo (MADRS scores 13.9±5.7 and 15.8±4.8 respectively, difference 1.89 [CI -2.7 to 6.5]: p=0.20) (Table 3 and Figure 2). ~~Although drop-out from the Sertraline group (n=7) was higher than from the placebo group (n=2), at baseline there was no difference between the groups in the MADRS (sertraline 24.1±3.3, placebo 21.5±2.1) or the BDI II (sertraline 24.0±5.3, placebo 29.0±9.5).~~

Eighteen patients experienced adverse events [24] and/or serious adverse events (SAEs) [13], nine in each randomised group. Infections (8) and nausea (4) were the most commonly reported adverse events. With regard to the SAEs, there was one death which was possibly related to the study medication as mentioned above, six SAEs which were unlikely to be related and six SAEs which were not related to the study medication.

Mean medication adherence among those who completed the study, estimated by a count of returned tablets, was 88% (range 46 – 100%). In only one was adherence (46%) less than 75%. Pre- and post-dialysis plasma sertraline blood levels were analysed after unblinding at the end of the study. Six patients were taking 100 mg daily. In one of these, levels were unmeasurable due to an interfering compound in the sample – possibly verapamil. Mean pre- and post-dialysis levels in the remaining five were similar at 32 ±12 ug/l and 34 ±18 ug/l respectively. The remaining two patients were taking 50 mg daily. In both of these, levels were <10 ug/l. One was 46% adherent on tablet count and the other 94% adherent.

Sixteen semi-structured interviews were conducted, 14 with trial patients and two with patients who had decided against entering the trial. No major issues were raised regarding trial format and procedures. However, both those not entering the trial and another who withdrew early, felt that they were not sufficiently depressed to warrant anti-depressants. They were reluctant to take further medication, citing current pill burden and concerns about becoming reliant on anti-depressants.

Discussion

Our results have confirmed that many patients on HD suffer from significant depression. A high proportion (32.3%) screened positive by BDI-II, of whom 46% had a past history of depression. In spite of this high prevalence, recruitment to the RCT was difficult. Over 70% of the 231 positively BDI-screened patients were ineligible or unwilling to consent to psychiatric interview. The commonest reason for non-eligibility (52%) was current anti-depressant medication and/or psychological therapy. A sizable proportion of those eligible for interview (38%) declined to participate. Data from the semi-structured interviews suggest that some patients felt insufficiently depressed to warrant further medication. There were also concerns about adding to already considerable pill-burdens and about becoming dependent on antidepressant drugs. Lack of patient equipoise may well have been a factor. The exclusion criteria we applied may also have been overly rigorous. These factors contributed to only 30 patients entering the RCT – only half the intended sample

size. Attention to these issues could inform design of a larger trial. ~~though unlikely to be limiting~~.

Other factors may also have relevance to the planning of a larger study. These include dropout rate and likely adherence to medication. Only 53% of patients on sertraline completed as opposed to 87% on placebo completed the study. There were five dropouts due to adverse events and SAEs, including one death, in the sertraline group compared to none in on placebo, indicating the possibility that sertraline may cause harm in this setting. Among those remaining in the study, adherence to the medication, assessed by pill counts and blood levels of sertraline, seems to have been adequate. We also confirmed that sertraline is not removed substantially by the haemodialysis procedure.

Depression scores (BDI-II and MADRS) improved significantly in both sertraline and placebo groups over 6 months. There was no significant difference between the groups. This may indicate a strong placebo effect, the effect of study participation (Hawthorne effect), or perhaps reflect the natural history of MDD in this setting. A major reason for performing the feasibility study was to evaluate variance in the clinical outcome measures (MADRS, BDI-II) to allow estimation of the effect size, to inform power calculations for a larger study. ~~However the only suggestion of an exploitable effect was the tendency for a higher rate of fall in MADRS scores in those on sertraline over the first two months (effect size 0.37), though the higher drop-out rate in this group could have influenced this. On this basis, to evaluate the potential advantage for sertraline over placebo at 2 months, assuming alpha=0.05 and 1-beta=0.90 with a one sided test, the required sample size would be 135 patients per study arm. If such a study were to be carried using the same inclusion/exclusion criteria as applied in this study and assuming the same the recruitment and retention characteristics, 3600 HD patients would need to be screened to achieve the recruitment target. We recognise though, that this may be a rather tenuous basis on which to plan a definitive study.~~ Our findings in this respect strongly suggest that, in planning a definitive study, a change of approach will be required, incorporating measures to increase eligibility, and improve participation and continuation in the study. Without such changes it may not be feasible to pursue a definitive study to answer this question.

~~There are a number design changes which might be considered in planning a larger study.~~ Inclusion/exclusion criteria could be amended to allow inclusion of patients currently taking antidepressants. This would entail stopping the antidepressant in clinically appropriate cases, followed by randomisation to either restarting antidepressant medication following a suitable washout period or continuing without it. If this were possible it would substantially reduce the number needing to be screened~~, though may be difficult to~~

~~manage and produce a distinctly heterogeneous study population~~. A shorter follow-up period of 2 to 3 months would reduce study costs but would be unlikely to reduce dropout rates since these mainly tended to occur early in the course of our study. As in the current study, depression should be diagnosed by diagnostic interview, rather than questionnaires, given the high degree of symptom overlap between depression and advanced kidney disease.

Our study has limitations, in particular, a small sample size. RCT recruitment was difficult and constrained by exclusion of the high number of patients a large proportion of whom were already receiving treatment for depression and reluctance of chronically ill patients to participate. Such problems have also hampered recruitment to trials of antidepressant medication in other chronic disease settings [28]. ~~These exclusions not only limited recruitment but also may have inadvertently introduced a selection bias in our sample.~~ Considering the feasibility design and the small sample size, the clinical outcomes we have described need to be interpreted with great caution. Nevertheless this feasibility study is the largest randomised trial of an anti-depressant in HD patients to date.

Current UK guidelines for treating depression in patients with chronic physical illness, issued by NICE, advocate pharmacological therapy for patients with MDD [19]. Our study raises concerns about the benefits and risks of this approach in patients on HD, a highly co-morbid group with a huge pill burden confounding their high prevalence of depression. Current practice patterns may be subjecting patients to substantial risk for little or no benefit. Identifying whether antidepressant medication is effective in this context is a major clinical need~~, hence the requirement for a definitive study~~. We agree with the European Renal Best Practice Group recommendations and those of a recent Cochrane review on the need for large well designed randomised studies of antidepressants versus placebo in this setting [8;18]. We acknowledge the difficulties of performing such a study in this population but in view of the current widespread use of antidepressants in this setting, the lack of evidence of efficacy, and the potential for adverse effects, it is important to find a way of carrying out such a study ~~if possible~~. Our findings may be helpful in its design.

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Declaration of Interests

The authors declare that they have no competing interests.

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Table 1: Exclusion criteria – medical conditions and contraindicated medication

Medical reasons	Hepatic impairment
	Hepatitis B & C
	HIV/AIDS
	Creutzfeldt-Jakob disease
	Pregnancy or childbearing potential and not using adequate birth control
	Psychiatric conditions, including substance dependency, psychosis, personality disorder, dementia or panic disorder, with the exception of other anxiety disorders.
Contraindicating medications	Monoamine oxidase inhibitors (MAOIs)
	Pimozide
	Triptans
	Antipsychotics
	Dopamine antagonists
	Tramadol
	Linezolid
	Warfarin

Table 2: Baseline characteristics

Parameters are estimated by the mean and standard deviation, median (25th, 75th centile), and by the number of events with a percentage for the group, as indicated for each parameter.

	Sertraline n=15	Placebo n=15
Age (years)	61.7 (13.2)	56.4 (14.4)
Male	11 (73%)	12 (80%)
Ethnicity	White 10 (67%) Asian 2 (13%) Black 2 (13%) Mixed 1 (7%)	White 8 (53%) Asian 4 (27%) Mixed 3 (20%)
Living conditions	Alone 5 (33%) With Partner 5 (33%) With Family 5 (33%)	Alone 5 (33%) With Partner 6 (40%) With Family 4 (27%)
Dialysis vintage (years)	3.1 (1.1, 6.2)	3.3 (1.1, 6.5)
Comorbidity (Charlson Index)	6.5 (5, 7)	6 (4, 6)
Diabetes	6 (40%)	7 (47%)
History of depression	5 (33.3%)	5 (33.3%)
Haemoglobin (g/L)	118 (19)	117 (14)
Urea (mmol/L)	44.8 (17.6)	44.0 (21.3)
Creatinine (mg/dl)	8.0 (3.2)	7.5 (3.6)
Kt/V (Last value at Month 1)	1.43 (0.36)	1.47 (.21)
Pre Dialysis BP systolic (mmHg)	148 (24)	147 (30)
Pre Dialysis BP diastolic (mmHg)	77 (9)	84 (19)

Table 3: Clinical Outcomes.

Mean (and standard deviation) values for the MADRS Score at 2, 4 and 6 months for the Sertraline and Placebo groups. The treatment effect is estimated as the difference between the observed outcome scores (with 95% confidence intervals) for the Sertraline and Placebo groups. As the difference between the groups was effectively zero at 6 months, no adjusted differences have been estimated. The change in the MADRS Score from baseline to 2, 4 and 6 months (with 95% confidence intervals) is also shown.

	N	Sertraline	N	Placebo	Between group difference
Baseline	15	24.5 (4.5)	15	25.3 (4.2)	
2 months	9	13.9 (5.8)	14	15.8 (4.8)	-1.9 (-6.5, 2.7)
Change from Baseline		-10.4 (-16.4, -4.4)		-8.9 (-13.3, -6.4)	
4 months	8	10.6 (6.6)	13	11.1 (5.5)	-0.45 (-6.0, 5.1)
Change from Baseline		-14.1 (-19.6, -8.6)		-14.8 (-18.1, -11.4)	
6 months	8	10.3 (5.8)	13	10.9 (5.1)	-0.67 (-5.7, 4.4)
Change from Baseline		-14.5 (-20.2, -8.8)		-14.9 (-18.4, -11.5)	

Figure 1. Trial Profile

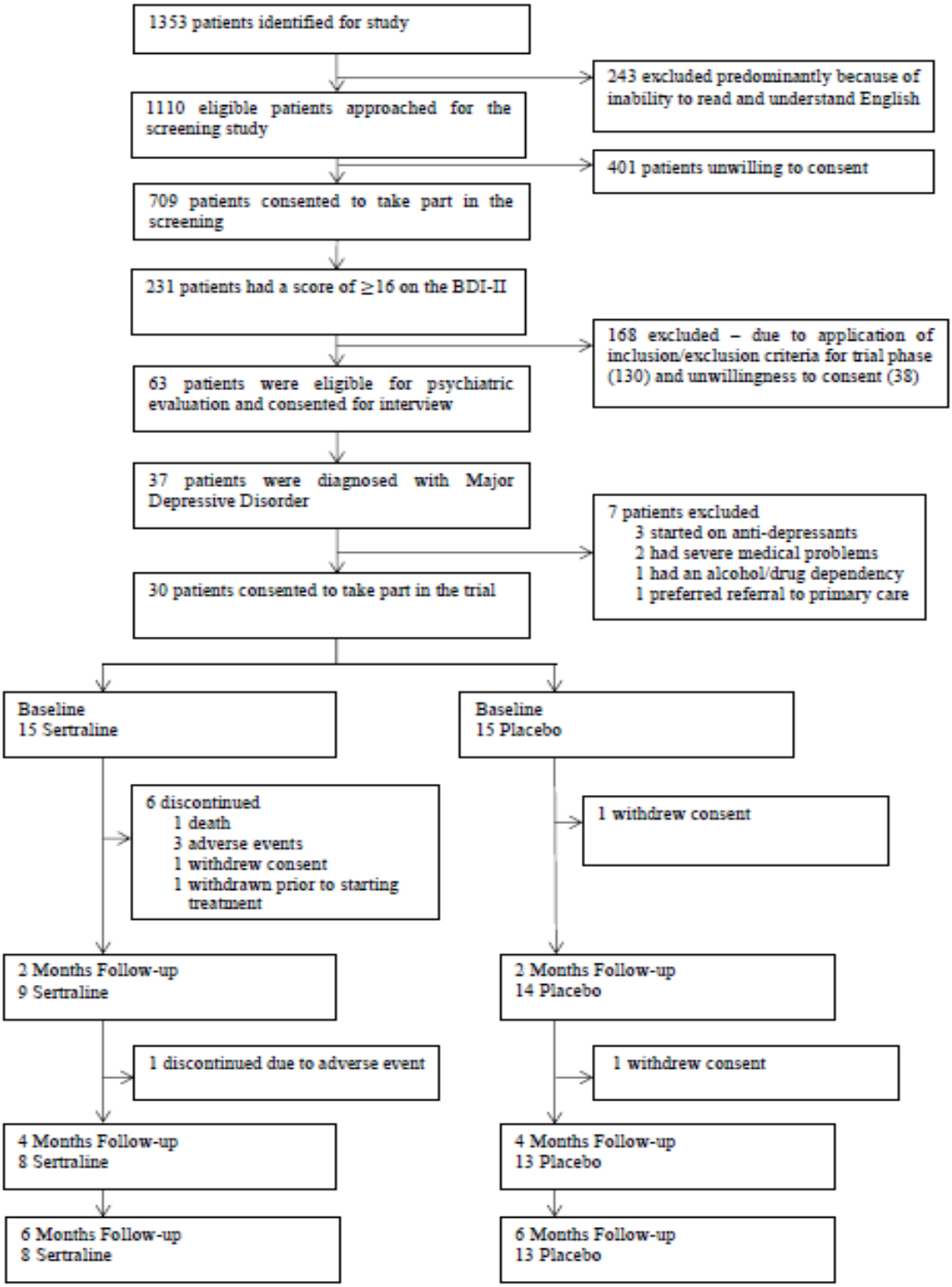
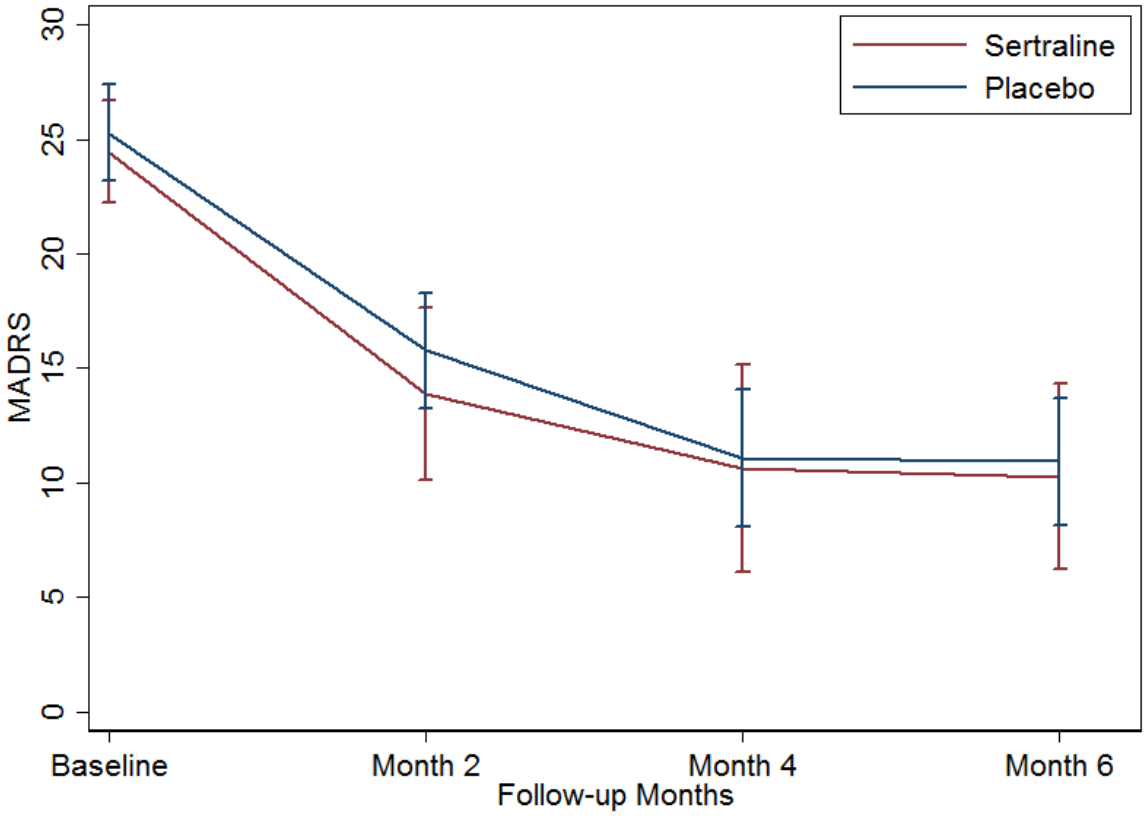


Figure 2. : MADRS scores over 6 months. The lines represent the Montgomery-Asberg Depression Rating Scale (MADRS) scores for the Sertraline (red) and Placebo (blue) groups at baseline, 2, 4 and 6 months. The 95% confidence intervals are estimated at each time point for both groups. The confidence intervals for the Sertraline group are larger at later time points due to the smaller group size.



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