Published in final edited form as:

J Neurol Sci. 2020 January 15; 408: 116563. doi:10.1016/j.jns.2019.116563.

MAMBO: Measuring Ambulation, Motor, and Behavioral Outcomes with Post-Stroke Fluoxetine in Tanzania: Protocol of a Phase II Clinical Trial

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Abstract

Background: Sub-Saharan Africa has a high stroke incidence and post-stroke morbidity. An inexpensive pharmacological treatment for stroke recovery would be beneficial to patients in the region. Fluoxetine, currently on the World Health Organization Essential Medicines List, holds promise as a treatment for motor recovery after ischemic stroke, but its effectiveness is controversial and untested in this context in Sub-Saharan Africa.

Aim: To determine if fluoxetine 20mg by mouth daily, given within 14 days of acute ischemic stroke, and taken for 90 days, is well-tolerated and safe with adequate adherence to justify a future randomized, controlled trial of fluoxetine in the United Republic of Tanzania.

Methods: Open-label, phase II clinical trial enrolling up to 120 patients. Participants will be recruited from the Muhimbili National Hospital in Dar es Salaam, Tanzania, and followed for 90 days.

The primary outcomes are: 1) safety, including serum sodium and hepatic enzyme levels, and 2) tolerability, as measured through study case report forms. The secondary outcomes are: 1) change in motor strength, as measured through the Fugl-Meyer Motor Scale, 2) adherence, as measured with electronic pill bottles, and 3) participant depressive symptom burden measured via standard questionnaires.

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Declaration of interest: The authors have nothing to disclose.

Conclusions: Expanding the evidence base for fluoxetine for Sub-Saharan African stroke survivors requires testing of its safety, tolerability, and adherence. Compared to prior studies in France and the United Kingdom, the patient characteristics, health infrastructure, and usual care for stroke recovery are substantially different in Tanzania. If fluoxetine shows favorable endpoints, scale up of its use post-stroke is possible.

Keywords

Stroke; fluoxetine; motor recovery; neuroplasticity; Africa; phase II clinical trial; ischemic stroke

1. Introduction and rationale:

There is an under-recognized and growing epidemic of stroke in Sub-Saharan Africa (SSA). Stroke is the leading cause of death and disability among all neurological disorders. Stroke is the second leading cause of death and disability globally and now accounts for more deaths than HIV/AIDS, malaria, and tuberculosis combined [1,2]. Approximately 85% of all strokes occur in low- and middle-income countries (LMICs) [1]. There are no proven pharmacological treatment options for post-stroke motor recovery; however, Sub-Saharan African populations could especially benefit from such treatment given their high post-stroke disability and a lack of available resources such as physical therapy [3-5].

Ischemic stroke doubles a patient's risk of dementia [6]. The burden of dementia is growing globally [7] and especially so in Africa, where the projected increase in dementia from 2001 to 2040 is 234% [8]. There is an urgent need for research that elucidates the major characteristics of dementia in aging African populations, especially in the context of stroke.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), may improve post-stroke motor recovery through its putative neuroplastic effects [9,10]. Such an effect is hypothesized to occur in addition to its recognized effects on treating post-stroke depression [11]. Since fluoxetine appears on the Essential Medicines List of the World Health Organization for depression, it is available, accessible, and affordable in countries across income levels. Despite favorable results of the 2011 FLAME study [12] of fluoxetine 20mg daily versus placebo on post-ischemic stroke motor recovery in France, the clinical use of post-stroke fluoxetine is not usual in SSA. The measured outcome in FLAME was the Fugl-Meyer Motor Scale (FMMS) score [13], a scale not typically used in clinical practice. FLAME included 118 patients. Recently, the FOCUS study [14], a large pragmatic study investigating fluoxetine use after acute, ischemic stroke in >3000 patients in the United Kingdom, reported results. Fluoxetine showed no beneficial impact on modified Rankin Scale scores at 90 days. An increase in bone fractures was reported. However, both FLAME and FOCUS included populations that are different than most stroke populations in SSA.

In Tanzania, stroke patients are overall younger, have a higher prevalence of hypertension, have a likely higher prevalence of HIV, and have little access to acute stroke and long-term rehabilitative services [3,15]. In higher-income settings, older patient age, access to higher-quality and urgent health care, and the varying endpoints may mitigate the understanding of post-stroke fluoxetine. These issues have led to the proposed study of fluoxetine in SSA. Here we report the protocol for MAMBO (Measuring Ambulation, Motor, and Behavioral

Outcomes with post-stroke Fluoxetine in Tanzania). In Swahili, “mambo” is used as a greeting, capturing our study question of whether fluoxetine will indeed introduce a new therapeutic option for stroke recovery for patients in SSA.

2. Methods:

2.1 Design:

MAMBO is single-group, open-label phase II clinical trial in adults with first-ever, new-onset ischemic stroke. Each participant meeting inclusion criteria will be given 20mg of fluoxetine by mouth daily for 90 days post-stroke. Participants will have cerebrospinal fluid drawn and cognitive screens performed to examine characteristics of incident post-stroke cognitive deficits in this setting.

2.2 Setting:

MAMBO will occur at the Muhimbili National Hospital (MNH), the largest referral and academic hospital in Tanzania. Participants will be recruited predominantly from the MNH neurology wards and the emergency department. MNH is publicly accessible and patients may self-refer or be referred by smaller hospitals as direct transfers. The first participant is anticipated to be enrolled in late 2019.

2.3 Aims:

The primary aim is to determine if fluoxetine 20mg daily, given within 14 days of new-onset, first ischemic stroke and taken for 90 days, will be 1) well-tolerated, and 2) safe, with 3) sufficient patient adherence to justify a future randomized, placebo-controlled trial in SSA. We hypothesize that fluoxetine will be well-tolerated, safe, and adhered to in the trial population.

An equal priority of MAMBO is to build neurological clinical trial research capacity at MNH. MNH employs 4 staff neurologists and serves as an epicenter for complex neurological care in Tanzania and the East African region. A final priority is to elucidate the extent of post-stroke cognitive deficits in this African population and to examine the associated biomarkers in patients who experience significant post-stroke cognitive decline.

2.4 Ethical Review:

This trial has been approved by the Partners Human Research Committee (PHRC) at Massachusetts General Hospital (IRB number: 2018P002441), the Institutional Ethical Review Board at Muhimbili National Hospital (IRB number: MNH/IRB/1/2018/191), and the National Medical Research Institute (NMIR/HQ/R.8a/Vol. IX/2272). The trial is registered with the Tanzanian Food and Drugs Authority (TZ19CT0012) and the U.S. National Library of Medicine at [ClinicalTrials.gov](https://clinicaltrials.gov) ().

2.5 Patient Population:

Ischemic stroke patients presenting to MNH above the age of 18 years, of any ethnic background, are eligible for enrollment. Enrollment is anticipated to approximate a 1:1 male to female ratio. Neither children nor pregnant women will be eligible given the unclear risk

of fluoxetine in these special groups. Additionally, the main mechanisms of stroke in children often differ (e.g. non-atherosclerotic etiologies) which are outside the scope of our study question.

Due to presumed differences in genetics, baseline prevalence of comorbidities, including HIV, and access to healthcare, the MAMBO patient population likely differs from that of similar studies' (FOCUS, FLAME) populations in higher-income countries. The difference may be significant enough to affect predictions of adherence and adverse event rates, thus the open-label nature of this phase II study, in which a primary aim is to determine whether it is feasible to conduct a future, placebo-controlled phase III trial of post-stroke fluoxetine in Tanzania.

2.6 Recruitment and Enrollment:

Patients presenting to MNH with new-onset stroke symptoms will be evaluated for participation in MAMBO using first-pass eligibility screening criteria (Table 1). First ever ischemic stroke will then be confirmed via a study-funded head computed tomography scan (CT), interpreted by the local investigative team. Although a head CT is the standard of care for stroke patients at MNH, in practice, many stroke patients lack the financial means to pay for the out-of-pocket expense of neuroimaging. Sub-classification of ischemic stroke will be based on the TOAST categorization [16].

In prior work in 2016 [15, 17], we found that approximately two stroke patients present to MNH daily, although admissions may reach up to six patients daily. Approximately 50% of strokes are ischemic at MNH, translating to approximately one eligible patient daily. Due to the dearth of stroke interventions available at MNH, we presume that most stroke patients will be interested in participating in this study. We do not anticipate public advertising or recruitment strategies outside of MNH to reach our target sample size. We anticipate recruitment will take approximately 6 months.

Following confirmation of first-ever ischemic stroke, study investigators will determine a patient's eligibility according to second-pass eligibility criteria. Study staff will administer questionnaires to collect the patient's health history (Table 2). Questionnaires reflect the Get with the Guidelines® survey intake forms of the American Heart Association, as modified by our team in preliminary studies. Participants will be clinically screened for dysphagia with a bedside swallowing screen to ensure they will be able to safely swallow pills [18]. Baseline motor capacity will be measured with the Fugl-Meyer Motor Scale by a physical therapist and/or physician with dedicated training in this scale. Video of the FMMS will be taken to ensure remote rating is possible post-assessment by other raters.

Fulfillment of second-pass eligibility criteria will prompt final determination of eligibility. Potential participants will have blood drawn (Table 3) to measure serum sodium concentration and hepatic enzyme levels (Table 1). Laboratory tests are based on the potential test abnormalities related to taking daily fluoxetine.

An eligible patient will be approached by a study physician who has no prior clinical connection to the patient and offered the opportunity to participate. Informed consent forms

will be provided in Swahili and/or English. The investigators do not anticipate prior familiarity between the study staff at MNH and the newly admitted patients since the hospital is large and patients will have new-onset disease. The investigators do not expect study procedures to impede usual care at MNH or pose a significant burden to usual operations.

Participants will be enrolled if they are additionally willing and able to (1) provide written consent personally or through a proxy, (2) follow up with the study team at 30, 60, and 90 days, and (3) undergo a clinical interview, physical examination, and laboratory studies by study investigators on the main outcomes of interest (Table 4). Participants must be geographically reachable and able to either return to MNH or have a study investigator complete a home visit at 90 days. Participants >100km away by land or residing on islands will be considered geographically unreachable.

Participants will be asked for contact information including their phone number and address. Three additional ways to contact the participant will be inquired including phone numbers of next of kin. Upon enrollment in to the study, participants will be assigned a unique numeric study ID and given a filled electronic pill bottle manufactured by Pillsy Inc.TM, a U.S.-based medical device company [19]. Electronic pill bottles with “smart caps” can record the time and date that the bottle caps are opened and closed by patients while at home. The opening and subsequent closing of the bottle is recorded as a medication use event and can be downloaded by the study team upon return of the pill bottles.

2.7 Study Procedures:

Participants will be examined at enrollment and followed at 30-, 60-, and 90-days post-enrollment. At each timepoint, safety assessments will take place (Table 4). The study endpoint is considered as the final safety assessments performed at the 90-day post-enrollment visit. Participants will be remunerated the equivalent of 400 USD per participant, or approximately 920,000 Tanzanian Shillings. It is anticipated that this sum will completely reimburse participant travel costs and lost income related to participation in the MAMBO study. Figure 1 depicts a participant’s flow through the study protocol.

2.8 Data Collection Methods:

All investigators will be trained on best practices for data collection and confidentiality before study commencement. Study data will be collected on paper records in English or Kiswahili and promptly uploaded to a password-protected REDCapTM database. All data collection forms will be anonymized and tracked using identification numbers to preserve participant privacy.

2.9 Intervention:

The primary intervention is 20mg daily fluoxetine for 90 consecutive days following ischemic stroke. Study drug will be provided by a U.S.-based medical pharmacy. Fluoxetine will be self-administered. Participants who are unable to self-administer will be offered the option of having a proxy administer the pills to them.

2.10 Primary outcomes:

The primary outcomes measured at the 90-day study visit will be the participant's tolerability and safety taking fluoxetine as evaluated by the number of reported adverse events on clinical case report forms and laboratory studies (serum sodium and hepatic enzyme levels) respectively.

2.11 Secondary outcomes:

Secondary outcomes will be adherence as evaluated through medication use data from the electronic pill bottles, change in participant motor impairment as measured through the change in FMMS at 90 days versus baseline visits, and participant depressive symptom burden as captured through the patient health questionnaire (PHQ-9) [20] and Montgomery-Åsberg Depressive Symptom Questionnaire [21].

2.12 Drop criteria:

Drop criteria are the following: 1) participants who develop a serious, non-stroke related disease, like myocardial infarction, that will threaten their life or seriously affect their medication regimen; 2) participants who are lost to follow-up, defined as not being available on three attempts at contact 3 days apart over the course of 9 days; and 3) participants who become pregnant.

If a participant fulfills any drop criteria, the Tanzanian site investigators will send a proposal, in writing, to the U.S.-site investigators to withdraw the participant from the study. The U.S.-site investigators will respond within 24 hours. When approved by the U.S.-site investigators, the participant will be formally withdrawn from the study and fluoxetine use will be discontinued. All reasonable efforts will then be made to collect the electronic pill bottle and any unused fluoxetine for safety and recording purposes. In cases where a participant develops a serious non-stroke related disease, he or she will be referred to the appropriate physicians at MNH. In cases of death or loss to follow-up, Tanzanian site investigators will make a reasonable attempt to discover the circumstances surrounding the participant withdrawal.

2.13 Data management:

De-identified data will be shared between the Tanzanian-site and U.S.-site investigators on at least a biweekly basis. An independent Data Safety Monitoring Board (DSMB) of international stroke and statistical experts will be appointed who will be responsible for scheduled review of all data related to the adverse events throughout the trial. The DSMB will include one Tanzanian expert as well as two international experts. The DSMB responsibilities will span the review of the research protocol and ongoing study activities, including the adequacy of participant recruitment and retention, data quality and completeness, safety-related events, and fidelity to the research study protocol. The DSMB will make recommendations to the study principal investigator concerning trial continuation, modification, or conclusion.

2.14 Statistical analyses:

The number of participants has been chosen based on the observed natural history of ischemic stroke in this setting [15, 22]. A post-stroke mortality of approximately 30% at 90 days is presumed. Of 120 enrolled participants, 84 are assumed to be alive at 90 days. We will consider the trial feasible if >50% of the patients have taken 80% of their fluoxetine and are evaluable at 90 days. With 84 patients, there is at least an 84% chance that we will meet this criterion, if the true proportion of adherent participants is 56%. The 50% and 80% benchmarks were chosen arbitrarily in this sample-size finding study. By contrast, if the true proportion of adherent patients is 40%, then there is <2.5% chance of meeting this criterion. With 120 enrolled patients, there is a 97% chance that we will see at least one occurrence of any event that would occur with a frequency of 3% in the study.

3. Discussion:

Stroke has reached epidemic proportions in Tanzania, as it has across SSA. Limited access to high-quality post-stroke care, including both acute thrombolytic agents and longer-term rehabilitative care, has led to significantly higher mortality rates than in the U.S. or Europe. The high stroke mortality in SSA has previously detracted from studies to improve the physical outcomes of stroke survivors. Tanzania has been the study location for multiple clinical trials for infectious and nutritional disorders as well as observational studies on stroke outcomes. MAMBO represents the first phase II study for a medication that could be pragmatically used post-stroke by Tanzanian patients.

The original FLAME study of post-stroke fluoxetine showed promising beneficial effects on motor recovery. Investigators in the UK, Sweden, and Australia have organized a trio of large, multinational, phase III clinical trials testing fluoxetine versus placebo post-stroke (the FOCUS, AFFINITY, and EFFECTS trials) [23]. The first of these trials to report results, the FOCUS trial of >3000 patients in the UK, found no significant improvement in motor outcomes of fluoxetine versus placebo. The treatment group experienced lower rates of post-stroke depression but higher rates of bone fractures, highlighting a potentially uncertain risk-to-benefit ratio of fluoxetine use post-stroke.

There are several important differences between MAMBO and FOCUS that prompt the MAMBO study to be performed despite the FOCUS results. First, stroke patients in Tanzania are on average much younger than stroke patients in the UK. In preliminary research [15] we found the average age of patients with stroke presenting to a large, urban hospital in Dar es Salaam Tanzania was 57 years. In comparison, the average age of patients enrolled in FOCUS was 71 years. Younger age is known to be a predictive factor for improved functional outcome and long-term survival in strokes [24, 25]. Increased age is also implicated in decreased neuroplasticity [26]. Evidence suggests that SSRIs facilitate neuroplasticity [27, 28]. It is possible that the favorable effects of post-stroke fluoxetine on motor recovery will be detectable in MAMBO's anticipated younger patient population versus the older FOCUS patients.

Second, stroke patients in Tanzania also have higher rates of HIV than patients in the UK. There is evidence that SSRI use improves HIV-associated neurocognitive impairment [29,

30], suggesting an SSRI-linked mechanism of neuroprotection that is separate from the ischemic context. It may be that patients with HIV respond favorably to post-stroke fluoxetine through this mechanism.

Third, the FOCUS trial used the modified Rankin Scale (mRS) as its primary outcome measure. The mRS is a pragmatic, straightforward assessment of disability that ranges from 0, no disability, to 6, death. Although easy to administer and widely understood by clinicians, the mRS may not capture meaningful differences in motor function that are relevant to a patient's quality of life. A wheelchair-bound patient will receive an mRS of 4, regardless of whether she can move her arms or not; yet arm function is certainly relevant to her life.

Finally, patients in the UK are wealthier and healthier than Tanzanian patients. They have access to acute thrombolytic treatments and rehabilitative care without out of pocket charges through the National Health Service; neither is standard in Tanzania, where patients who wish to receive rehabilitative care generally must pay out of pocket for the service and thrombolytic agents are entirely unavailable at public hospitals[31]. There may also be genetic differences between UK and Tanzanian populations that affect stroke recovery or neuroplasticity [32, 33]. It is possible that, in higher-income settings, the overall better health of patients combined with ready access to acute and long-term stroke care dampen the favorable effects of post-stroke fluoxetine. The significant differences—location, typical patient age, sample size, outcome measures, and study phase—between MAMBO and ongoing and reported studies in the UK, Sweden, and Australia underscore a lack of direct comparability with remaining equipoise.

A potential limitation of this study is the absence of a minimum score on the FMMS required for inclusion in MAMBO. Although a requirement for enrollment is upper-extremity motor weakness attributable to stroke on neurological exam, a minimum FMMS score was not required for inclusion. It was deemed infeasible to conduct a full FMMS examination on every potentially eligible stroke patient at MNH. It is possible that we will overestimate the adherence rates and feasibility of a future phase III clinical trial by enrolling patients with high FMMS scores who are more easily capable of staying adherent. Here the investigators deemed it more important to capture the full range of adherence data across ischemic strokes of differing severities. If adherence differs by baseline upper-extremity Fugl-Meyer scores, this will be reported. The electronic pill bottles will be especially useful for understanding this potential issue.

MAMBO is the first interventional trial of a pharmacological treatment for post-stroke motor recovery in Tanzania. It will provide new information on the adherence, follow up, and mortality of stroke survivors in this large Tanzanian referral center. It will build a Tanzanian-U.S. collaborative team for future randomized, controlled trials to improve neurological outcomes in SSA. Finally, it will provide novel data on post-stroke dementia and cognitive changes in Tanzanian patients.

Acknowledgements:

We are grateful to Professor David Schoenfeld at Harvard Medical School for statistical discussions. We thank Dr. Jefferey Gluckstein, Neurology Resident at Partners Neurology, for participating in the capacity building efforts at Muhimbili National Hospital.

Funding: The MAMBO trial is funded by an R21 grant from the National Institutes of Health [Project Number: 5R21TW011051]. The funder had no role in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the article for publication.

References:

- [1]. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol* 2017;16:877–897. [PubMed: 28931491]
- [2]. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1260–1344. [PubMed: 28919118]
- [3]. Walker RW, Viney R, Green L, et al. Trends in stroke admissions to a Tanzanian hospital over four decades: a retrospective audit. *Trop Med Int Health* 2015;20:1290–1296. [PubMed: 25983015]
- [4]. Stenumgård PS, Rakotoniranaivo MJ, Sletvold O, et al. Stroke in a resource-constrained hospital in Madagascar. *BMC Res Notes* 2017;10:307. [PubMed: 28738901]
- [5]. Ezejimofor MC, Uthman OA, Maduka O, et al. Stroke survivors in Nigeria: A door-to-door prevalence survey from the Niger Delta region. *J Neurol Sci* 2017;372:262–269. [PubMed: 28017225]
- [6]. Leys D, Henon H, Mackowiak-Cordoliani M-A, Pasquier F. Poststroke Dementia. *Lancet Neurol*. 2005;4(4):752–759. [PubMed: 16239182]
- [7]. Norrving B, Kissela B. The global burden of stroke and need for a continuum of care. *Neurology*. 2013;80(3):S5–S12. [PubMed: 23319486]
- [8]. Guerchet M, Akinyemi R, Paddick SM, Wimo A, Prince M; for Alzheimer's Disease International. The epidemiological evidence: prevalence, costs, incidence, mortality and risk factors. In *Dementia in sub-Saharan Africa: Challenges and opportunities (16-40)*. Alzheimer's Disease International 2017 9.
- [9]. Lee JY, Lee HE, Kang SR, et al. Fluoxetine inhibits transient global ischemia-induced hippocampal neuronal death and memory impairment by preventing blood-brain barrier disruption. *Neuropharmacology* 2014;79:161–171. [PubMed: 24316161]
- [10]. Ng KL, Gibson EM, Hubbard R, et al. Fluoxetine Maintains a State of Heightened Responsiveness to Motor Training Early After Stroke in a Mouse Model. *Stroke* 2015 ;46:2951–2960. [PubMed: 26294676]
- [11]. Fruehwald S, Gatterbauer E, Rehak P, et al. Early fluoxetine treatment of post-stroke depression--a three-month double-blind placebo-controlled study with an open-label long-term follow up. *J Neurol* 2003;250:347–351. [PubMed: 12638027]
- [12]. Chollet F, Tardy J, Albucher J-F, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol* 2011;10:123–130. [PubMed: 21216670]
- [13]. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehabil Neural Repair* 2002;16:232–40. [PubMed: 12234086]
- [14]. FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *Lancet* 2019;393:265–274. [PubMed: 30528472]
- [15]. Regenhardt RW, Biseko MR, Shayo AF, et al. Opportunities for intervention: stroke treatments, disability and mortality in urban Tanzania. *Int J Qual Health Care* 2019;31:385–392. [PubMed: 30165650]

- [16]. Adams HPJ, Bendixen BH, Kapelle LJ, et al. Classifications of subtype of acute ischemic stroke: Definitions for Use in a Multicenter Clinical Trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41. [PubMed: 7678184]
- [17]. Saadi A, Okeng'o K, Biseko MR, et al. Post-stroke social networks, depressive symptoms, and disability in Tanzania: A prospective study. *Int J Stroke* 2018;13:840–848. [PubMed: 29676225]
- [18]. Palli C, Fandler S, Doppelhofer K, et al. Early dysphagia screening by trained nurses reduces pneumonia rate in stroke patients: A clinical intervention study. *Stroke* 2017;48:2583–2585. [PubMed: 28716980]
- [19]. Pillsy | 24x7 Digital Medication Coach, with smart pill bottle and app [Internet]. Available from: <https://www.pillsy.com/>
- [20]. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med*. 2001;16:606–613. [PubMed: 11556941]
- [21]. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9. [PubMed: 444788]
- [22]. Okeng'o K, Chillo P, Gray WK, Walker RW, Matuja W. Early Mortality and Associated Factors among Patients with Stroke Admitted to a Large Teaching Hospital in Tanzania. *J Stroke Cerebrovasc Dis*. 2017;26(4):871–878. [PubMed: 27913201]
- [23]. Mead G, Hackett ML, Lundström E, et al. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicentre randomised controlled trials. *Trials*. 2015 20;16:369.
- [24]. Weimar C, Ziegler A, König IR, Diener HC. Predicting functional outcome and survival after acute ischemic stroke. *J Neurol*. 2002;249(7):888–895. [PubMed: 12140674]
- [25]. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. *Stroke*. 2003 1;34(1):122–126. [PubMed: 12511762]
- [26]. Spriggs MJ, Cadwallader CJ, Hamm JP, Tippet LJ, Kirk IJ. Age-related alterations in human neocortical plasticity. *Brain Res Bull*. 2017;130:53–59. [PubMed: 28043855]
- [27]. Pinto CB, Saleh Velez FG, Lopes F, et al. SSRI and Motor Recovery in Stroke: Reestablishment of Inhibitory Neural Network Tonus. *Front Neurosci*. 2017;11:637. [PubMed: 29200995]
- [28]. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. *Neurosci Biobehav Rev*. 2017;77:317–326. [PubMed: 28342763]
- [29]. Sacktor N, Skolasky RL, Moxley R3, et al. Paroxetine and fluconazole therapy for HIV-associated neurocognitive impairment: results from a double-blind, placebo-controlled trial. *J Neurovirol*. 2018;24(1):16–27. [PubMed: 29063516]
- [30]. Ances BM, Letendre SL, Alexander T, Ellis RJ. Role of psychiatric medications as adjunct therapy in the treatment of HIV associated neurocognitive disorders. *Int Rev Psychiatry*. 2008;20(1):89–93. [PubMed: 18240065]
- [31]. Berkowitz AL, Mittal MK, McLane HC, et al. Worldwide reported use of IV tissue plasminogen activator for acute ischemic stroke. *Int J Stroke*. 2014;9:349–55. [PubMed: 24207029]
- [32]. Stewart JC, Cramer SC. Genetic Variation and Neuroplasticity: Role in Rehabilitation After Stroke. *J Neurol Phys Ther*. 2017;41 Suppl 3:S17–S23. [PubMed: 28628592]
- [33]. Alawieh A, Zhao J, Feng W. Factors affecting post-stroke motor recovery: Implications on neurotherapy after brain injury. *Behav Brain Res*. 2018;340:94–101. [PubMed: 27531500]

Highlights

- We present the protocol of a phase II trial of post-stroke fluoxetine in Tanzania
- Fluoxetine is an inexpensive antidepressant that is widely accessible globally
- Fluoxetine has shown mixed results in post-stroke motor recovery in high-income countries

Figure 1:
Flowchart of recruitment, enrollment, and study procedures for the MAMBO study

Table 1

Inclusion and exclusion criteria for participants in the MAMBO trial.

First pass inclusion criteria	First-pass exclusion criteria	
1. Age 18 and <80 years in Tanzania	1. NIH Stroke Scale Score >20 points	5. Recent history of head trauma
2. First stroke with symptoms <14 days prior	2. Unconscious at presentation	6. Baseline motor deficits from other etiologies
3. Upper extremity motor weakness on examination attributable to stroke, as captured through a standard neurological evaluation	3. Current antidepressant or psychoactive drug use (e.g. SSRI, MOA inhibitor, benzodiazepine)	7. Moribund and unlikely to survive to 90 days
	4. Current pregnancy	
Second pass inclusion criteria	Second-pass exclusion criteria	
1. CT-confirmed ischemic stroke	1. Hemorrhagic conversion of ischemic infarct	
	2. Dysphagia preventing swallowing of a pill	
	3. CT-confirmed hemorrhagic stroke	
	Third-pass exclusion criteria	
	1. Renal impairment (creatinine >180 micromol/L or GFR <30mL/min/1.73m ²)	3. Hyponatremia (<125mmol/L), or hepatic impairment (serum ALT > 120U/L)
	2. Transient ischemic symptoms	

Table 2.

Selected baseline variables

Demographic Data	Clinical Data
<ul style="list-style-type: none"> • Participant name • Date of birth • Gender • Health insurance status • Race • Home status 	<ul style="list-style-type: none"> • Final clinical diagnosis related to stroke <ul style="list-style-type: none"> – Ischemic stroke – Transient Ischemic Attack – Subarachnoid hemorrhage – Intracerebral hemorrhage – Stroke not otherwise specified • Previous medical history <ul style="list-style-type: none"> – Atrial fib/flutter – CAD/prior MI – Carotid stenosis – Current pregnancy – Depression – Diabetes mellitus – Dyslipidemia – Migraine – Obesity – Previous stroke – Smoker • Ambulatory status prior to event • Initial NIH stroke scale score • Initial exam findings • Ambulatory status upon admission • Antiplatelet/anticoagulant medication use • Brain imaging • Vital signs

Table 3

Blood tests to be performed pre- and post-enrollment for participants in MAMBO.

Blood tests to be performed prior to	
•	Sodium
•	Potassium
•	Alanine aminotransferase
•	Alkaline phosphatase
•	Creatinine
•	Beta-Human Chorion Gonadotropin in women
Blood tests to be performed following enrollment	
•	CD4 count
•	HIV viral load (HIV ELISA and Uni-Gold™)
•	Hemoglobin A1c %

Table 4

MAMBO study visit procedures.

Visit	Procedures
Baseline Visit	<ul style="list-style-type: none"> • 10-15mL blood draw • Lumbar puncture to draw cerebrospinal fluid • Serum sodium and hepatic enzyme level (ALT, alkaline phosphatase) • Evaluation of motor function through the Fugl-Meyer Motor Scale • Evaluation of disability through the modified Rankin Scale (mRS) • MRI brain • Cognitive testing with the MoCA and IDEA screens
30-day study visit & 60-day visit	<ul style="list-style-type: none"> • 10-15mL blood draw • Serum sodium and hepatic enzyme level (ALT, alkaline phosphatase) • Download medication adherence data from electronic pill bottles • Inquiry to adverse events • Evaluation of disability through the modified Rankin Scale (mRS)
90-day final study visit	<ul style="list-style-type: none"> • 10-15mL blood draw • Serum sodium and hepatic enzyme level (ALT, alkaline phosphatase) • Download medication adherence data from electronic pill bottles • Inquiry to adverse events • Evaluation of disability through the modified Rankin Scale (mRS) • MRI brain • Cognitive testing with the MoCA and IDEA screens • Assessment of depressive symptoms through PHQ-9 and Montgomery-Åsberg Depression Scale • Evaluation of motor function through the Fugl-Meyer Motor Scale