Phase Two Randomized Controlled Crossover Trial of Atomoxetine to Treat Memory Impairment due to Multiple Sclerosis
PI: James Sumowski, PhD
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Icahn School of Medicine at Mount Sinai
Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital
Mount Sinai Queens
New York Eye and Ear Infirmary
of Mount Sinai
Mount Sinai St. Luke's
Mount Sinai West

Program for the Protection of Human Subjects
Institutional Review Boards

Mount Sinai Health System
One Gustave L. Levy Place, Box 1081
New York, NY 10029-6574
T 212-824-8200
F 212-876-6789
irb@mssm.edu
icahn.mssm.edu/pphs

Amendment
IRB-16-01030
James Sumowski

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1. Modification

Summary of the Modification Request

We have a simple modification: changing the verbal memory test that we are using as our screening tool. We proposed using the California Verbal Learning Test, Second Edition (CVLT-II). We want to change this to the Rey Auditory Verbal Learning Test (RAVLT). Both are published validated memory instruments. (We have gone through the protocol and changed the CVLT-II to the RAVLT. This is the only change we made.)

Justification for the Modification

We believe the RAVLT will be more sensitive to memory deficits than the CVLT-II, as the normative data for the RAVLT is more appropriate for our sample (better matched for level of education).

This Modification Changes the Consent Document or Information that May Affect Subjects' Willingness to Continue to Participate in the Research	No
Subjects Will Be Re-Consented or Provided with the New Information	No

Explanation Why Re-Consenting or Providing Subjects with the New Information is Not Necessary

This is a very minor change, which does not affect the consent form or patient burden (time or effort).

2. Summary - Title

Protocol Title

Phase Two Randomized Controlled Crossover Trial of Atomoxetine to Treat Memory Impairment due to Multiple Sclerosis

Principal Investigator	James Sumowski
Primary Department	Neurology
Application Initiated By	James Sumowski

Lay Summary

Approximately half of persons with multiple sclerosis (MS) develop memory dysfunction, which makes it difficult to maintain gainful employment, manage a household, and lead a fully-engaged social life. There are currently no validated symptomatic treatments for memory deficits in persons with MS. We will perform a pilot fourteen-week double-blind cross-over phase-two randomized controlled trial (RCT) of atomoxetine (80mg qd) versus placebo to improve memory in MS patients with documented memory impairment. Atomoxetine is a non-stimulant selective norepinephrine reuptake inhibitor FDA-approved to treat cognitive-behavioral symptoms of attention deficit / hyperactivity disorder (ADHD; Strattera, Eli Lilly). Pre-clinical evidence suggests that atomoxetine may also improve memory by targeting brain mechanisms responsible for memory function (norepinephrine in the hippocampus). Twenty-four MS patients demonstrating objective memory impairment on neuropsychological screening tests will be randomly assigned to once-daily orally-administered atomoxetine or identically-encapsulated placebo for the first phase, followed by a two-week washout period, and then six weeks of the cross-over condition. The RCT will be performed at the Corinne Goldsmith Dickinson Center for MS at the Icahn School of Medicine at Mount Sinai. Baseline and follow-up evaluations will assess change on Primary Outcomes (objective memory function on neuropsychological tests and patient-reported memory change) and Secondary Outcomes (additional objective and self-reported memory measures; objective and self-reported cognitive efficiency measures; fatigue and mood). We predict that atomoxetine will lead to significantly greater improvements in Primary and Secondary memory outcomes relative to placebo. Consistent with the ADHD literature, there may be additional effects of atomoxetine versus placebo on Secondary cognitive efficiency outcomes. Results of this trial will inform decisions / planning for a possible phase 3 trial, which may ultimately support the use of non-stimulant, once-daily atomoxetine as a memory treatment option for MS patients.

IF Number IF1930708

3. Summary - Setup

Funding Has Been Requested / Obtained	Yes
Application Type	Request to Rely on Mount Sinai IRB
Research Involves	Prospective Study ONLY
Consenting Participants	Yes
Requesting Waiver or Alteration of Informed Consent for Any Procedures	No
Humanitarian Use Device (HUD) Used Exclusively in the Course of Medical Practice	No
Use of an Investigational Device to Evaluate Its Safety or Effectiveness	No
Banking Specimens for Future Research	No
Cancer Related Research that Requires Approval from the Protocol Review and Monitoring Committee (PRMC).	No

Is this Cancer Related Research? Cancer Related Research is defined as research that has cancer endpoints or has a cancer population as part of or all of its targeted population. This includes protocols studying patients with cancer or those at risk for cancer.

Clinical Trial Yes

**** A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).***
**** Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.***

Drugs / Biologics Yes

**** Drugs / Biologics That Are Not a Part of Standard Practice***
**** Controlled Substances***
**** Drugs / Biologics Supplied by the Research Sponsor or Purchased with Study Funds***

Ionizing Radiation for imaging or therapy, including X-Ray, Fluoroscopy, CT, Nuclear Medicine, PET andor Radiation Therapy:

*** Purely for standard of care:**	
*** In frequency or intensity that exceeds what is necessary for standard of care:**	No

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Hazardous Materials No

**** Recombinant DNA***
**** Viral Vectors***

**** Plasmids***
**** Bacterial Artificial Chromosomes***
**** Toxic Chemicals, Potentially Toxic Medications, Carcinogens***
**** Autologous Cell Lines***

Request Use of Clinical Research Unit Resources No

4. Summary - Background

Objectives

1. Investigate whether treatment with atomoxetine (versus placebo) improves (a) memory on objective cognitive tasks and (b) patient-reported memory in MS patients with documented memory impairment.

2. Investigate whether atomoxetine (versus placebo) also has beneficial effects on (a) cognitive efficiency on objective cognitive tasks, (b) patient-reported attention/organization, and (c) fatigue and mood.

Background

Memory Impairment in Multiple Sclerosis: Most persons with multiple sclerosis (MS) are diagnosed between ages 20 and 40,[1] while they are striving to finish education, establish careers, and manage households. About half of MS patients will suffer memory decline,[2-4] which begins early in the disease[4,5] and negatively impacts quality of life (e.g., unemployment).[3,6] Despite the high prevalence and debilitating consequences of memory decline in MS patients, there are currently no validated symptomatic memory treatments.[7-9] We have reported preliminary support for levo-amphetamine (l-AMP) as an effective memory treatment in MS, with memory-impaired patients showing a 50% improvement on objective memory tasks relative to placebo,[10] with no effects on processing speed.[11] It is instructive that l-AMP, classified as a stimulant, improved memory rather than speed. Although both stimulants, l-AMP and dextro-amphetamine (d-AMP, prescribed for ADHD) have different mechanisms of action: d-AMP works on dopaminergic targets in the frontal lobe (e.g., striatum) to increase attention, whereas l-AMP targets norepinephrine pathways, with a greater impact on hippocampal structure and memory in rodents.[12] Unfortunately, l-AMP is not FDA-approved for any indication, and there is no industry support to perform the necessary phase 3 trials required for FDA approval. As such, l-AMP is not a viable option for treatment of MS memory impairment; however, the aforementioned preliminary data on l-AMP and memory provide critical guidance toward an even more promising non-stimulant option: atomoxetine.

Atomoxetine and Memory: Atomoxetine (Strattera, Eli Lilly) is a non-stimulant selective norepinephrine reuptake inhibitor FDA-approved for treatment of ADHD.[13] Neuropharmacologically, atomoxetine leads to increased norepinephrine in the cortex and hippocampus, without increases in dopamine within the striatum or nucleus accumbens,[14,15] which explains reduced risk of locomotor activation and addiction / abuse when using atomoxetine versus stimulant medication (e.g., methylphenidate, for review[16]). Clinical trials in ADHD have understandably focused on outcomes of inattention and hyperactivity; however, positive effects of atomoxetine on visual memory have also been reported,[17] consistent with (a) positive effects on memory in rodents,[18] (b) the importance of norepinephrine for memory generally,[19] and (c) human cerebral blood flow evidence showing that atomoxetine differentially increases mesial temporal blood flow relative to placebo and methylphenidate.[20]

Atomoxetine as a Memory Treatment in MS: MS patients experience hippocampal atrophy beginning early in the disease,[21-23] histological studies document substantial hippocampal demyelination and synaptic loss,[24-26] and work from our group and others has linked MS memory deficits with hippocampal structure and function (e.g., [21,27-30]). Consistent with aforementioned roles of atomoxetine on hippocampal norepinephrine and memory, and preliminary effects of l-AMP on memory in MS[10] (likely via norepinephrine[12]), there is adequate evidence to support a pilot clinical trial of norepinephrine reuptake inhibition with atomoxetine as a potential symptomatic treatment of memory impairment in MS. An important practical consideration supporting this proposal is that atomoxetine is already FDA-approved, so the path to clinical use for memory impairment in MS patients is more straightforward. Finally, there are important physiological, psychological, and regulatory barriers to stimulant medication use, which are circumvented by use of the non-stimulant atomoxetine.

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Primary and Secondary Study Endpoints

PRIMARY ENDPOINTS:

1. Memory will be assessed as a mean normative z-score across verbal and spatial memory tasks: (a) Selective Reminding Test (SRT) Total Learning, (b) SRT Delayed Recall, (c) Brief Visuospatial Memory Test, Revised (BVMT-R) Total Learning, (d) BVMT-R Delayed Recall. Memory will be measured at three points: Baseline (day prior to phase one [treatment or placebo]), Treatment Follow-Up (last day of atomoxetine), and Placebo Follow-up (last day of placebo). (These will be known as phase one and phase two follow-ups initially, as treatment or placebo will only be revealed after the study is complete.) Alternate forms of the tests will be used.

2. Patient-Reported Memory Change: Patients will endorse global memory change over the past month as: much improved (3), improved (2), slightly improved (1), unchanged (0), slightly worse (-1), worse (-2), much worse (-3). This will occur twice: at the phase one and phase two follow-ups.

SECONDARY ENDPOINTS:

1. At the same three time points above (baseline, phase one follow-up, phase two follow-up), we will administer two additional memory tasks:
(a) CANTAB Paired Associate Learning (PAL, Total Errors Adjusted); (b) NIH Toolbox Picture Sequence Memory Test (PSMT; raw score).

2. Patient-Reported Memory Change: The Perceived Deficits Questionnaire (PDQ) will be administrated at the same three time points. Retrospective Memory and Prospective Memory subscales will be derived at each time point.

3. At the same three time points, we will measure performance on four cognitive efficiency tasks assessing processing speed (Symbol Digit Modalities Test, Oral Version: Total Correct), sustained attention/continuous performance (CANTAB Rapid Visual Information Processing: RVP A'), reading comprehension speed (Woodcock Johnson Reading Fluency), and working memory (WAIS-IV Digit Span: total raw score).

4. Patient Reported Outcomes of (a) cognitive efficiency assessed with Attention and Planning/Organization subscales of the PDQ; (b) fatigue assessed with the Fatigue Severity Scale; (c) mood assessed with the Beck Depression Inventory Fast Screen, and (d) suicidal ideation with the Columbia Suicide Severity Rating Scale.

Protocol Was Already Approved by the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB) Under a Different Principal Investigator	No

Protocol Was Previously Submitted to an External(non-ISMMS) IRB	No

5. Research Personnel

Name/Department	Role/Status	Contact	Access	Signature Authority	Phone	Email
James Sumowski / Neurology	Principal Investigator /		Signature Authority			
Christina Lewis /	ARC /		Edit Access			
Ilana Katz Sand /	CI /		Edit Access			
Gabrielle Pelle /	ARC /		Edit Access			

6. Sites

Site Name	Icahn School of Medicine at Mount Sinai
Other External Site Name	
Contact Details	
Approved	
Approval Document	
Funded By Mount Sinai	
Other IRB	

7. Subjects - Enrollment

Site Name	Icahn School of Medicine at Mount Sinai
Subjects To Be Enrolled	
30	
Total Number of Subjects to be Enrolled Across All Listed Sites Above (Auto Populated)	30

8. Subjects - Populations

Inclusion Criteria

1. Diagnosis of Multiple Sclerosis based on the Revised McDonald criteria (Polman. Ann Neurol 2011; 69: 292-302)

2. Age 21 - 60 years.

3. Memory Impairment on validated neuropsychological memory screening tests, as follows:
a) performance #16th percentile on both Rey Auditory Verbal Learning Test (RAVLT) Total Learning and WMS-IV Visual Reproduction (Immediate); and
b) mean normative performance is at least 1.0 standard deviation below expectations based on premorbid IQ (WTAR provides estimates of expected memory function).

4. Patient self-report of memory decline from previously higher level of functioning.

Exclusion Criteria

1. Current stimulant medication usage.

2. Previous diagnosis or treatment for ADHD or any neurologic condition other than multiple sclerosis (e.g., traumatic brain injury, epilepsy)

3. clinical relapse of MS within 60 days of screening,

4. change in disease-modifying therapy within 90 days of screening,

5. below average estimated premorbid intelligence (WTAR score #16th percentile),

6. severe cognitive impairment indicated by a Mini Mental Status Examination (MMSE) < 24/30,

7. contraindications for atomoxetine use: (a) self-reported history of suicidal ideation within the last twelve months (Columbia Suicide Severity Rating Scale), (b) diagnosis of bipolar illness, (c) moderate or severe current depressive symptomatology (Beck Depression Inventory Fast Screen # 9), (d) diagnosis of hepatic disease, (e) narrow angle glaucoma, (f) pheochromocytoma, (g) monoamine oxidase inhibitor within 14 days of study drug start, (h) taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine), (i) diagnosis of heart disease, (j) pregnant or planning pregnancy during the study period, (k) breastfeeding, (l) hypersensitivity to atomoxetine or component of formulation. Note that in the case where a potential subject is receiving medication for care that interacts with atomoxetine, her / his clinical regiment will not change to allow for study entry.

Enrollment Restrictions Based Upon Gender, Pregnancy, Childbearing Potential, or Race	Yes

Justify Restriction(s)

We are excluded women who are pregnant or planning to become pregnant during the study period. Pregnancy risk associated with atomoxetine is category C (risk cannot be ruled out).

Age Range(s)	18 to 64 Years
Targeted Population(s)	Adults - Patients

Other Aspects that Could Increase Subjects Vulnerability

None.

Safeguards to protect Subjects rights and welfare

We are employing inclusion / exclusion criteria which minimize risk to patients from atomoxetine, and we will monitor side effects. We will also emphasize the voluntary nature of this study, and that there is no penalty for withdrawal.

9. Subjects - Participation

Duration of an Individual Subjects Participation in the Study

Once consented and screened, the baseline will be completed and the rest of the study will take fourteen weeks: six-week phase one, two-week washout, six-week phase two.

Duration Anticipated to Enroll All Study Subjects

One year

Estimated Date for the Investigators to Complete This Study Within one year

Procedures for Subjects to Request Withdrawal

Subjects who desire to discontinue participation in this study will contact the study coordinator via telephone or email to withdraw.

The information collected prior to subject withdrawal may be used if deemed necessary to complete the study. As an FDA regulated study, the data cannot be destroyed. Data will not be distributed to anyone.

Procedures for Investigator to Withdraw Subjects

The investigator will withdraw subjects who fail to complete the baseline or follow-up evaluation, or who report serious side effects of the study medication as determined by Co-I Ilana Katz Sand, M.D. (attending MS neurologist).

The information collected prior to subject withdrawal may be used if deemed necessary to complete the study, unless the subject informs us in writing that they withdraw the data collected and the samples collected. Previously collected data can only be withdrawn if it has not yet been de-identified and distributed.

Participants Will Be Recruited Yes

Recruitment Method(s) Clinical Practice

How Participants Will Be Identified

Patients meeting inclusion criteria for age and MS diagnosis will be as asked by their treating physician, nurse practitioner, or neuropsychologist if they would be interested in hearing more about the study. If the patient is interested in participating and reports subjective difficulty with memory, a member of the research team will either speak with them in person, or they will be asked if they want to be contacted by a member of the research team at another time, or they will be given contact information for a member of the research team. If the patient is interested and would prefer to be contacted, the clinician will provide us with the name and best way to contact them. We also have a list of patients who have asked us to contact them if we have any enrolling research studies. We will contact those patients at their preferred contact.

Who Will Initially Approach Potential Participants Member of Primary Care Team, Treating Physician

How Research Will Be Introduced to Participants

Patients will be asked by their physician, nurse practitioner, or neuropsychologist if they are interested in learning about a placebo-controlled RCT of a drug aiming to improve disease-related memory decline. Patients will be told that atomoxetine is a non-stimulant drug FDA-approved to treat ADHD, but that the use of atomoxetine to treat memory deficits is not an approved use of the drug. Patients will be told that it is a cross-over design, and that they will receive atomoxetine during one phase, and placebo during the other, but that he/she will not be blinded to phase. If they are interested, patients will be referred to the study personnel as noted above.

How Participants Will Be Screened

Inclusion and exclusion criteria will be reviewed with patients via telephone or in-person screening with study personnel. Patients who report memory difficulties and meet demographic eligibility criteria will be invited to the MS Center for a brief twenty-minute in-person screening. After informed consent, the screening will include two memory screening tests (RAVLT, WMS-IV Visual Reproduction), a word-reading estimate of premorbid IQ (WTAR), a depression screening tool (BDI-FS), and an assessment of suicidal ideation with the past six months (Columbia Suicide Severity Rating Scale). Demographic (e.g., age) and medical (e.g., last relapse) will be reviewed with the patient and/or their medical record. All current medications will be recorded, and Co-I Ilana Katz Sand, M.D. will review for possible interactions with atomoxetine.

10. Procedures - Narrative

Description of the Study Design

This is a double-blind randomized placebo-controlled cross-over design whereby each of 24 enrolled MS patients (meeting inclusion criteria / screening) will complete the following:
1. Baseline Evaluation (neuropsychological, psychological, self-report, and motor assessment; about 1 hour).
2. Phase One Drug: Six weeks of treatment with atomoxetine or placebo (randomly assigned)
3. Phase One Evaluation: baseline evaluation repeated on the last day of phase one.
4. Two week washout period
5. Phase Two Drug: Six weeks of opposite condition as phase one (i.e., if atomoxetine in phase one, then placebo in phase two)
6. Phase Two Evaluation: baseline evaluation repeated on the last day of phase one.

Description of Procedures Being Performed

After informed consent, subjects will engage in a 30-minute screening consisting of memory tests (Rey Auditory Verbal Learning Test, Visual Reproduction of the Wechsler Memory Scale, Fourth Edition), word-reading test (Weschler Test of Adult Reading), depressive symptoms (Beck Depression Inventory, Fast Screen), and assessment of suicidal ideation within the past twelve months (Columbia Suicide Severity Rating Scale).

Patients who meet all inclusion criteria will advance to the fourteen week crossover trial.

1. Baseline Evaluation:
a. Memory Tests: Selective Reminding Test, Brief Visuospatial Memory Test, Revised, CANTAB Paired Associate Learning, NIH Toolbox Picture Sequence Memory Test (PSMT)
b. Cognitive Efficiency Tests: Symbol Digit Modalities Test, CANTAB Rapid Visual Information Processing, Woodcock Johnson Reading Fluency, WAIS-IV Digit Span
c. Questionnaires: Perceived Deficits Questionnaire (self-report of cognitive/memory deficits), Beck Depression Inventory, Fast Screen (mood), Fatigue Severity Scale (fatigue), Columbia Suicide Severity Rating Scale (suicidal ideation)
d. Motor Tasks: 25-foot walk, Nine Hole Peg Test

2. Phase One Drug:
Patients will receive atomoxetine or identically encapsulated placebo from the research pharmacy. They will receive two containers: one containing seven 40mg capsules, and one containing enough 80mg capsules for the remaining five weeks. Subjects will be instructed to take the 40mg dose once per day (in the morning) for the first seven days, and then switch to the 80mg dose once per day (in the morning) for the remainder of Phase One. Subjects will be encouraged to set an alert in their smartphones to remind them to take the capsule at the same time each day. Subjects will also be provided with information about atomoxetine (Strattera) provided by the pharmaceutical company (Eli Lilly). Patients will be instructed not to take more than one capsule per day. If they miss a dose, they should keep it in the container. All remaining capsules will be returned to the investigator at the end of the six weeks (when the subject returns for the first follow-up). Patients will also be instructed to contact the study team immediately if they experience any side effects.

3. Phase One Evaluation: The baseline evaluation will be repeated on the last day of Phase One. Alternate forms will be used as appropriate. In addition, patients will be asked to guess which type of capsule they were tasking, and also complete an additional questionnaire:
Patient-Reported Memory Change: Patients will endorse global memory change over the past month as: much improved (3), somewhat improved (2), mildly improved (1), unchanged (0), mildly worse (-1), somewhat worse (-2), much worse (-3).

4. Two week washout period.
Patients will go two weeks without taking any study capsule.

5. Phase Two Drug
The same procedures as Phase One will be followed, except that patients will receive the opposite capsules as Phase One.

6. Phase Two Evaluation
The same procedures as the Phase One Evaluation will be repeated.

Description of the Source Records that Will Be Used to Collect Data About Subjects

Paper source records will include demographic information, general medical history, and MS medical history information; however, there will be no PHI on any source forms. All data will be collected using paper neuropsychological record forms and/or score sheets. CANTAB tasks are performed on an iPad; however, no PHI will be entered into the iPad. Instead, CANTAB scores will be transferred to paper score sheets. All data will be entered into a RedCap database, which will include no PHI.

Description of Data that Will Be Collected Including Long-Term Follow-Up

This is documented above.

Research Requires HIV Testing

11. Procedures - Genetic Testing

Genetic Testing Will Be Performed No

Guidance and Policies > Future Use Data Sharing and Genetic Research

12. Procedures - Details

Surveys or Interviews Yes

Type of Instruments Being Used Standardized, Created By Research Team

Names of Standardized Instruments

NEUROPSYCHOLOGICAL INSTRUMENTS
Rey Auditory Verbal Learning Test
Visual Reproduction of the Wechsler Memory Scale
Brief Visuospatial Memory Test, Revised
Selective Reminding Test
CANTAB Paired Associate Learning
NIH Toolbox Picture Sequence Memory Test
Symbol Digit Modalities Test
CANTAB Rapid Visual Information Processing
Woodcock Johnson IV Reading Fluency
Wechsler Adult Intelligence Test, Third Edition: Digit Span
Wechsler Adult Reading Test
25-Foot Walk
Nine Hole Peg Test

QUESTIONNAIRES
Perceived Deficits Questionnaire
Beck Depression Inventory, Fast Screen
Fatigue Severity Scale
Columbia Suicide Severity Rating Scale

Description of Instruments Created By Research Team

Patient-Reported Memory Change: Patients will endorse global memory change over the past month as: much improved (3), improved (2), slightly improved (1), unchanged (0), slightly worse (-1), worse (-2), much worse (-3).

Audio / Photo / Video Recording No

Deception No

Results of the Study Will Be Shared with Subjects or Others No

13. Procedures - Instruments

Instruments Created By Research Team

Type	Questionnaire
Name	Patient Reported Memory Change
Upload	MEMORY QUESTIONNAIRE.docx
Type	Questionnaire (Revised)
Name	Patient Reported Memory Change
Upload	Memory Questionnaire Revised.docx

14. Procedures - Compensation

Compensation for Participation	Yes
Type	Check
Amount Per Visit	10
# of Visits	1
Line Total	10
Justification	Time
Who Will Pay	
Specify Who Will Pay	
Comment	
For completion of baseline evaluation	
Type	Check
Amount Per Visit	20
# of Visits	1
Line Total	20
Justification	Time
Who Will Pay	
Specify Who Will Pay	
Comment	
For completion of Phase One Follow-up	
Type	Check
Amount Per Visit	20
# of Visits	1
Line Total	20
Justification	Time
Who Will Pay	
Specify Who Will Pay	
Comment	
For completion of Phase Two Follow-up	
Total Compensation	50

PI must attest that all of the following are true.
**** Credit for payment accrues as the study progresses.***
**** Payment is not contingent upon completing the entire study.***
**** The amount of payment and the proposed method and timing of disbursement is neither coercive nor presented undue influence.***
**** Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.***
**** All information concerning payment, including the amount and schedule of payments, is in the informed consent document.***
**** Compensation does not include a coupon good for a discount on the purchase price of the product once it has been approved.***

15. Consent - Obtaining Consent

Consent Process Adult Consent

Where and When Consent Will Be Obtained

Consent will be obtained in the Corinne Goldsmith Dickinson Center for MS (MS Center) at Mount Sinai (FPA)

Waiting Period for Obtaining Consent

The study will be discussed with potential subjects prior to the day of the study, and persons will be given a copy of the consent form to review at home before deciding whether to participate. The study and consent form will be discussed with potential subjects again on the day they come in for the study, and they will have an opportunity to ask questions. Only then will the consent form be signed and the study begin.

SOP HRP-090 Informed Consent Process for Research Is Being Used Yes

PPHS Worksheets, Checklists and SOPs

Process to Document Consent in Writing Will Use Standard Template

Non-English Speaking Participants Will Be Enrolled No

Justification for Not Enrolling Non-English Speaking Participants

The neuropsychological assessment tools used for this trial are validated in English only.

16. Consent - Documents

Consent Documents

Type	Informed Consent Form
Name	ICF v1.0
Upload	Sumowski_ICF_revised_clean.doc

Consent Templates

17. Data - Collection

Health Related Information Will Be Viewed, Recorded, or Generated Yes

Description of Health Information That Will Be Viewed, Recorded, or Generated

Medical History: information required to determine study eligibility (see inclusion criteria), such as a history of depression or other mood disorder, ADHD, or neurologic disease other than MS. We will also document current medications.

MS History: Medical information directly related to MS, including the type of MS (e.g, relapsing, progressive), last clinical relapse of MS, history of MS medication, current levels of MS disability (e.g., neurologic exam on record)

Performance on neuropsychological, psychological, and motor tasks described above.

Non-Health Related Information Will Be Viewed or Recorded Yes

Description of Non-Health Information That Will Be Viewed or Recorded

Demographic information: age, sex, education, primary language, maternal education, occupation, race, ethnicity (required for reporting purposes for grant-funding agency)

Note that identifiable information checked below (e.g., name, MRN, address, etc.) will be used to maintain contact with the subject, to complete required forms for reimbursement, and/or confirm medical history. Identifiable information will also be kept separate from study data, as noted above.

HIV / AIDS Related Information Will Be Viewed or Recorded No

Data That Will Be Viewed, Recorded, or Generated Contains ANY of the Following Directly Identifiable Information Yes

Will Be Viewed Name, Social Security Number, Medical Record Number, Address by street location, Telephone number, Geographical Subdivisions Smaller Than a State, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date), Email Address

Will Be Recorded Name, Social Security Number, Medical Record Number, Address by street location, Telephone number, Geographical Subdivisions Smaller Than a State, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date), Email Address

Data Collection Sheet

A Data Collection Sheet is required if you are either performing a retrospective review, or your study meets the category of exempt 4 research, or your study meets the category of expedited 5 research. Please upload it here.

Data Collection Source(s) Participant, Medical Chart (Paper or Electronic)

18. Data - HIPAA

Obtaining HIPAA Authorization Yes

How PHI Will Be Protected from Improper Use or Disclosure

Study data will include no direct identifiers, and a unique number assigned to each patient. Study data will be kept in a locked filing cabinet in the PI's office, and kept separate from the subjects' signed consent forms (also in a locked cabinet). A list of subject-number pairings will also be in a locked filing cabinet, and only the PI and the study team will be assess to these cabinets.

PHI Will Be Destroyed at the Earliest Opportunity Consistent with the Research Yes

When and How PHI Will Be Destroyed

PHI will be destroyed at the completion of the study by shredding documents with PHI, which are otherwise in locked filing cabinets. The key linking the study data (in RedCap) to PHI (e.g., consent forms) will be destroyed at the end of the study, so that PHI (and patient identities) cannot be linked back to the study data. Only the de-identified study data will be needed for publication. Signed consent forms with HIPPA waivers (unlinked to data) will be kept for six years following completion of the study, and then destroyed via shredding.

PHI Will Be Shared No

PI must attest to the following.

**** I assure that the protected health information (PHI) will not be disclosed to any other person or entity not listed on this form except where required by law or for the authorized oversight of this research project. If at any time I want to reuse this PHI for other purposes or disclose it to other individuals or entities I will seek approval from the IRB.***

19. Data - Storage

Location Where Data Will Be Stored

Data will be stored in a locked filing cabinet located in a locked closet, within a locked office (PI: JF Sumowski). Each lock has a separate key.

How will the data be stored?	With a Code That Can Be Linked to the Identity of the Participant
Research Personnel Responsible for:	James Sumowski
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Christina Lewis
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Ilana Katz Sand
Accessing Data	
Receipt or Transmission of Data	
Holding Code That Can Be Linked to Identity of Participants	
Research Personnel Responsible for:	Gabrielle Pelle
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes

Duration Data Will Be Stored

Raw data will be stored for three years following completion of the study. Non-identifiable data in the form of a database (RedCap) will be kept indefinitely.

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission

Data will be stored in a locked filing cabinet located in a locked closet, within a locked office (PI: JF Sumowski). Each lock has a separate key. Only two persons have the key to the filing cabinet: JF Sumowski (PI) and the study research coordinators. Data files will be kept separate from identifiable data (PHI), with the exception of a password protected and encrypted Excel file linking subject names and subject numbers. This file will be located on a ISMMS network drive and only accessed from ISMMS computers. Only JF Sumowski and the coordinators will have the password. Raw data files may be retrieved by JF Sumowski or the research coordinator, and viewed on site in a private office space. Files will not be removed from Mount Sinai Hospital. Files will be immediately returned to their secure location within the filing cabinet.

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)

JF Sumowski will lead statistical analyses, which will consist of dependent T-tests comparing differences in outcomes (e.g., memory composite score) between the drug and placebo phases of the cross-over trial.

20. Data - Safety Monitoring

More Than the Minimum Data Safety Monitoring Will Be Done Yes

Principal Monitor Ilana Katz Sand

Additional Monitors

Specific Items That Will Be Monitored for Safety

Suicidal ideation will be monitored with the Columbia Suicide Severity Rating Scale. Subjects who report suicidal ideation at any point in the study will be escorted to the psychiatric emergency department at Mount Sinai Hospital for further evaluation.

Suicidal ideation and other adverse events reported by patients will be recorded. Co-I Ilana Katz Sand, M.D. will review all adverse events as they are reported, and judge severity. Dr. Katz Sand is not involved in data collection or processing, so she can be unblinded to identify whether adverse events occurred during atomoxetine or placebo.

Frequency of Data Review

Suicidal ideation will be evaluated at baseline, first follow-up, and second follow-up for all subjects, and immediate action will be taken if suicidal ideation is present (as noted above).

Dr. Katz Sand will also be told immediately of any other serious adverse events, such as allergy to atomoxetine. She will have access to condition assignments in the case of adverse events.

Rules for Alteration of Study Design

After twelve subjects have been completed the trial, Dr. Katz Sand will evaluate whether serious adverse events are more likely during atomoxetine or placebo. If serious adverse events are 2:1 more likely during atomoxetine, the study will be halted.

Selection Procedures to Minimize Toxicity

We are using the recommended dosage of atomoxetine based on prescribing information in the package insert. Also, we are excluding patients taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine), which minimizes risk of toxicity.

Grading System to Evaluate Adverse Events

Serious adverse events will include suicidal ideation and allergy to atomoxetine.

Other adverse events include constipation, upset stomach, difficulty sleeping, dry mouth, loss of appetite, irregular periods, decrease in sexual function, urinary hesitancy sweating, and dizziness.

Procedures to Assure Data Accuracy

All adverse events reported to the research team at any time in the study (including the three assessment phases) will be recorded for frequency and severity. Severity will be judged my our study physician, Ilana Katz Sand, M.D. These will be documented in a study RedCap database, and will be reported for each condition (atomoxetine, placebo) with the study results. Dr. Katz Sand will also be able to determine subject condition in the event of serious adverse events.

Suspension Reported to

Suspension would be reported the the IRB.

Anticipated Circumstances of Subject Withdrawal

Subjects would be withdrawn from the study if they experience any severe adverse events. Of course, subjects may choose to withdraw at any time without penalty.

Primary or Secondary Safety Endpoints

Primary safety outcome will be suicidal ideation.

Secondary safety endpoints include constipation, upset stomach, difficulty sleeping, dry mouth, loss of appetite, irregular periods, decrease in sexual function, urinary hesitancy sweating, dizziness, and allergy to atomoxetine.

Data Monitoring Committee Description DMC.docx

DMC Charter Available No

Will the Research Include Data Coordinating Center Activities?

21. Funding

Funding Source Name	National Multiple Sclerosis Society
Contact	
Funding Category	Foundation
	Meditrack (https://contracts.tractmanager.com/Contracts/Login.aspx)
Grant or Contract Title	Pilot Randomized Controlled Trial of Atomoxetine to Treat Memory Impairment in MS Patients
Grant or Contract Number	PP-1606-24739
Funding Status	Funded
Project Initiated By	Investigator
Grant / Contract Principal Investigator (PI)	James Sumowski
Department	Neurology
Department	Neurology
Phone	
Email	james.sumowski@mssm.edu
Protocol and Funding Proposal Match	No
Identify Substantive Differences Between Protocol and Funding Proposal	We changed the trial from a parallel design to a cross-over design to improve statistical power. As such, we lowered our sample size from 30 to 24. All other aspects (e.g., hypotheses, doses, outcomes, etc.) are the same.

22. Drugs / Biologics

Study Fund Account (or alternate departmental / fund account, if study is not yet established)

Select One:

A fund number is required before the IDS will sign off on any forms or initiate any procedures. For those studies which an alternate departmental fund number is provided, IDS will delay billing by 6 months.

Add all drugs and biological agents whose use is specifically prescribed in the research. This includes approved drugs that are supplied or paid for by the company for this research, approved drugs that are not given under routine care guidelines, and all investigational drugs. Approved drugs whose use is up to the discretion of an attending physician as part of medical care do not need to be added. Contact the Investigational Drug Service (IDS) if unsure http://www.mssm.edu/ids .

To be completed by Pharmacy staff upon review of the protocol:

FYI: NO ACTION REQUIRED
IDS FEE SCHEDULE
Review: ___
Initiation:___
Dispensation:___
Maintenance:___
Special Compounding:___
Coordinating Center:___
Close-Out:___

23. Financial Administration

This information will help the Financial Administration of Clinical Trials Services (FACTS) office determine whether a Medicare Coverage Analysis (MCA) is needed for the research study. If you have any questions while completing this form, please contact the FACTS office at (212) 731-7067 or FACTS@mssm.edu.

Clinical Research Study Category Investigator Initiated

Payment Options:
**** Option 1: No protocol-required services will be billed to patients or third-party payers. Does Not Need MCA***
**** Option 2: Protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Must Have MCA***
**** Option 3: Study is initiated and federally funded by a Government Sponsored Cooperative Group who will only pay for services that are solely conducted for research purposes and other protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Billing Grid Only Required, NO MCA***
**** Option 4: Study involves only data collection and has no protocol-required clinical services. Does Not Need MCA***
**** Option 5: Study is not described in any of the above options. Please describe the study and specify whether External Sponsor (i.e., industry, government, or philanthropic source) and/or patient/third party payer will pay for protocol required services. MCA MAY Be Required***

Payment Option Option 1

No MCA is needed per option selected above.

Payment Option 1:
**** Option 1A: Department/collaborating departments will act as internal sponsor paying for all protocol-required services and no protocol-required services will be billed to patients or third party payers.***
**** Option 1B: Study involves protocol-required clinical services and an External Sponsor (i.e., industry, government, or philanthropic source) will pay for all protocol-required services.***

Payment Option 1 Option 1B

24. Attachments

Type	Name	Version	Status	Filename	Uploaded Date
Other - Other IRB Correspondance	RAVLT	1	New	RAVLT.pdf	02/23/2017
Package Insert Document (DRUG NAME)	strattera-pi.pdf	1	New	strattera-pi.pdf	02/26/2017