

CLINICAL STUDY PROTOCOL

Study Title: **Treatment of Restless Leg Syndrome (RLS) Augmentation with Ecopipam, a D1 Specific Antagonist**

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STUDY SYNOPSIS

This is an exploratory study, the first ever designed specifically to treat augmentation, designed to assess gross tolerability and obtain data for a power analysis and other study design features in subsequent studies, if a signal is detected. A cross-over design was selected over an open label study specifically to blindly document the effect of D1 antagonist removal. It is not at all known if there will be a carry-over effect, immediate return of symptoms, rebound exacerbation, etc. Future studies could assess the ability to discontinue the D2 agonist, the ability to prevent augmentation in DA treated patients, and the assessment of a D1 antagonist to treat de novo RLS.

Project specific aim: (1) To determine the mechanism of dopaminergic induced augmentation and if a D1 antagonist drug can improve augmentation symptoms.

Background and Rationale for the Objectives

Dopamine agonists can dramatically treat restless legs syndrome (RLS) and periodic limb movements (PLMS). However chronic use often results in augmentation, a condition manifest by earlier onset and intensification of the original RLS symptoms. Understanding and eliminating augmentation is probably the greatest practical problem in RLS management.

The specific mechanisms by which dopaminergics treat RLS at all, is not established. There are, however, several clues. First, stimulation of dopamine type 2 and 3 receptors robustly and immediately (first dose) improve RLS, suggesting dopamine receptors are directly involved. Next, leg involvement more than arm involvement, strongly suggests spinal cord involvement. RLS and PLMS seen in spinal cord lesions, which subsequently improve with dopamine agonists (DA), suggest the DA may be stimulating receptors in the spinal cord. Circadian RLS symptoms (worse at night) suggest strong regulation by circadian centers, and the unpleasant sensation/urge suggests impaired nociceptive function. We, and subsequently others, have proposed involvement of the dopaminergic A11 diencephalic-spinal tract, which is the main source of spinal dopaminergic innervation in the rat, mouse, non-human primate, and probably human.

The pathophysiology of augmentation is entirely unknown. Simple explanations invoke a “down regulation” of dopamine receptors, but this occurs within days of any exogenous dopaminergic supplementation, whereas clinical augmentation occurs linearly over years. L-dopa causes augmentation much more rapidly than dopamine agonists. This has been ascribed to its shorter half-life, however this concept has been questioned because longer acting and shorter acting DAs seem have similar rates of augmentation. L-dopa has several differentiating features compared to DA, but one of the greatest is its higher affinity to D1 receptors.

We developed an animal model of RLS consisting of iron deprivation and lesioning of the A11 dopaminergic neurons that descend into the spinal cord, where they interact with both D1 subtype and D2 subtype receptors. These animals showed markedly increased activity c/w RLS. Importantly this phenotype improved with D2/3 agonists and worsened with D2/3 antagonists. However, the most dramatic pharmacologic effect was a surprising worsening with a D1 agonist, suggesting opposite effects of D2 and D1 family receptors on the model. In later experiments we tried to identify underlying mechanisms of augmentation by treating some modeled mice chronically with the D2/3 agonist pramipexole, and

comparing spinal cord neurotransmitter and receptor profiles against untreated model and control mice. In the treated RLS animals, neither spinal dopamine neurotransmitters, nor iron were reduced. However, chronic use did increase affinity of the D1 receptors. There was also a mild reduction in D3 receptor density.

In retrospect, the marked differences in D1 and D2 properties should not be surprising. D1 have opposite effects in the basal ganglia, where excitatory D1 receptors are prominent in the “direct pathway” and inhibitory D2 receptors in the “indirect pathway.” Stimulation of D1 and D2 receptors in the spinal cord has also shown opposite effects on locomotion and rhythmic activity in normal and spinal cord lesioned animals. D2 agonists suppress these rhythmic movements whereas D1 agonists increase rhythmic movements, possibly analogous to PLMS. In these animals, this mimics the effects of low dose dopamine, via L-dopa, (inhibited rhythmic movement) and high dose dopamine, increased movements. Dopamine has greater D2 affinity than D1 but at higher doses stimulates D1 receptors robustly. Anecdotally, this also mimics the effects of increasing L-dopa doses in augmented RLS patients, which is inevitably and rapidly unsatisfactory. In contrast, carefully increasing dose and timing of dopamine agonists (which have less D1 affinity) can be a successful strategy for many years, before eventually failing in many subjects.

We propose that augmentation is caused by gradual affinity change in D1 receptor density/affinity and subsequent stimulation of these receptors worsen RLS. At the same time, D2/D3 stimulation continues to treat RLS symptoms, resulting in the inherently unstable clinical scenario of augmentation, and the severe exacerbation of RLS after DA withdrawal.

Ecopipam (Psyadon Pharmaceuticals,) is a D1 specific antagonist, in fact the only D1 specific antagonist to undergo major human trials, with good CNS penetration and long T1/2 (8-15 hours). The drug has been tested in >1,000 subjects and has undergone Phase 2/3 trials for Tourette’s syndrome, obesity, schizophrenia, cocaine dependency, Lesch Nyhan disease, and diabetes mellitus. Doses range in these trials was 10-200 mg/day, but receptor saturation is thought to occur rapidly at doses of 100 mg/day. Safety profile has been good with sedation being the most common (potentially desirable in this population) adverse event.

Study Aims/Objectives

Aim 1

To determine the mechanism of dopaminergic induced augmentation and if a D1 antagonist drug can improve augmentation symptoms

Study Design

This is a double-blind, exploratory proof of concept, cross-over trial of the D1 antagonist ecopipam for subjects with augmented RLS. We prefer a cross-over compared to open label because we desire a blinded drug withdrawal. We will recruit 10 subjects taking dopamine agonists for RLS who are currently experiencing augmentation. Problematic augmentation will be assessed using the Augmentation Severity Rating Scale (ASRS). The goal is to have 8 completers. There is no power analysis as this is an exploratory study and there is no previous data on treatment of augmentation. “Meaningful improvement” is not even

established. A safety analysis will be done after 5 subjections have been enrolled by Psyaden Pharmaceuticals Inc. Duration of study and is based mostly on contracted drug availability for this pilot study.

Protection of Human Subjects

This study will be conducted in accordance with:

- Principles of the Declaration of Helsinki (revised version of Seoul, Korea, October of 2008).
- Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonization (ICH) Guideline, Topic E6, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) – Protection of Human Subjects and Part 56 – Institutional Review Boards.
- Health Insurance Portability and Accountability Act (HIPAA), and all other applicable local regulatory requirements and laws.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s) in accordance with GCP.

Informed Consent and HIPAA Compliance

No study-specific procedure will be undertaken on an individual patient until that patient or the patient's legally authorized representative has given written informed consent to take part in the study. The consent for storage will include consent to access stored data.

It will be made clear to each potential participant that informed consent may be withdrawn at any time without needing to give a reason and that such withdrawal will not compromise the relationship between the patient and the Investigator or the Institution nor the patient's future treatment.

Informed consent will be obtained in accordance with US 21 CFR 50.25 and ICH Good Clinical Practice. Applicable HIPAA privacy notifications will be implemented and HIPAA authorizations signed before protocol procedures are carried out. Information will be given in both oral and written form.

Consent forms will be in a language fully comprehensible to the prospective patients and/or their legally authorized representatives. Patients, their relatives, guardians, or legally authorized representatives will be given ample opportunity to inquire about the details of the study. Prior to a patient's participation in the study, the written informed consent form should be signed and personally dated by the patient or by the patient's legally authorized representative, and by the person who conducted the informed consent discussion. Patients or their legally authorized representatives will be provided a copy of the signed informed consent form.

Competency will be determined based on the individual's ability to understand the study as outlined

in the consent form: the procedures, the potential risks posed to them, the lack of direct benefit to them, and their ability to withdraw from the study at any time without repercussion. If the subject is unable to indicate that they understand the study in its entirety, they will be deemed not competent to consent to the study.

Consent will be obtained from subjects or their proxies by the principal investigator or his designees, fully trained to obtain written informed consent for research and explicitly listed in the study delegation log. Each of these individuals will have extensive clinical and research experience. Participants will be offered the option to speak with a PI if any questions remain. At each research visit, study staff will review the purpose of and procedures involved in this study with the patient volunteering for the study.

Potential Risks and Benefits

Potential Risks

Ecopipam has not been used specifically in patients with RLS. When tested in other conditions, e.g. diabetes, Tourette's syndrome, obesity, and cocaine dependency, the only side effect that was seen more often than in patients taking placebo was somnolence. Other reported side effects include sedation, nausea, lightheadedness, insomnia, back pain, euphoria, and rarely headache. It is not known exactly how Ecopipam will affect RLS, either at start or discontinuation.

Potential Benefits

There may be no benefit to the subject. The subject may experience benefit in their RLS symptoms, which be temporary or for a longer duration. The subject may benefit from the knowledge that this study could improve our understanding of RLS.

Statement of Non-Participation

The alternative to participation in this study is not to participate in it and obtain treatment off-study with available therapies.

Patient Confidentiality (HIPAA)

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). According to those regulations, the consent form for the study includes the content of the HIPAA Authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of research subjects to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient

authorization.

For additional information on subject confidentiality, see below the section on Data Storage and Management. Signed consent forms will be kept in paper format and stored in a locked cabinet in the PI offices. All other forms needed for the study will be available electronically in a secure web site, so that testing can be entered using any encrypted, lockable computer, tablet (device) or phone with a browser function. For analyses, all data will be stored de-identified in a secure database.

Subject Screening

We will recruit up to 10 subjects with a goal of 8 completers. Study candidates will be screened for inclusion and exclusion criteria by any member of the study team. Those who meet criteria and consent to the study will be enrolled. If no consent provided, the patient will not be enrolled and the reason for their non-participation included with the date of screening.

Eligibility Criteria

Inclusion Criteria

- Provide consent to participate in the study
- Individuals of either sex, 21-85~~9~~ years of age
- Clinically defined Restless Leg Syndrome, and problematic augmentation currently on dopaminergic treatment.
- Subjects with reproductive capability including all males and women of child-bearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable)

Exclusion Criteria

- Current use of Opioid medications
- Clinical relevant depression or other medical problems that in the opinion of the investigator would not allow for safe completion of the protocol.
- Suicidal ideation
- History of epilepsy
- Current MAO inhibitors
- History of hepatic or renal impairment
- Women who are pregnant or breastfeeding

Study Procedures

Our aim is to determine the mechanism of dopaminergic induced augmentation and if a D1 antagonist drug can improve augmentation symptoms. Subjects will be randomized to Ecopipam or placebo for 5 weeks/arm in two periods with a 2-week washout period in between. Total time for subject participation is

approximately 13 weeks.

Medical History

The history will center on risk factors and symptoms or disorders relevant to neurological disorders.

Physical and Neurological Examinations

Brief standard neurological examinations will be done similar to that of a normal clinic visit. Laboratory assessments of serum chemistry and a 12-lead ECG will be conducted on the first day (before initiating treatment) and the last day of treatment of each crossover phase (i.e. Ecopipam or placebo).

At each Visit subjects will undergo:

- Verification of continued trial participation
- Assessment of overall wellness with query for adverse events and safety reporting
- Clinical Global Impressions and safety calls at week 1 and 3 of each arm, and 1 week after withdrawal) of each arm.
- Completion of following instruments:
 - International RLS Rating Scale,
 - Augmentation Severity Rating Scale,
 - Epworth Sleep Scale,
 - Hamilton Depression Scale,
 - MOS Sleep Scale,
 - Fatigue Severity Scale, and
 - Montreal Cognitive Assessment
 - Columbia Suicide Assessment Scale.
 - Vital signs and examination
- Education on and/or review of the 24-hour RLS Symptom diary to be kept just prior to starting each arm and just before ending each arm. Analysis will be last observation carried forward.

Concurrent Medications for RLS

The following medications are allowed dopamine agonists (pramipexole, ropinirole, rotigotine)
The following medications are prohibited: dopamine antagonists, anti-histaminergic medications. In addition, Ecopipam has been shown a competitive inhibitor for CYP2D6 at nanomolar concentrations, and as such, the use of strong CYP2D6 inhibitors (i.e. Fluoxetine, Paroxetine, Bupropion, Quinidine, Cinacalcet and ritonavir) are prohibited.

Schedule of Events:

Study procedures (Per patient)	Baseline Screening Visit: Day -14 to 0	Visit 1: Day 0	Phone Call 1: Day 8	Visit 2: Day 15	Phone Call 2: Day 22	Visit 3: Day 36	Phone Call 3: Day 43	Visit 4: Day 50	Phone Call 4: Day 57	Visit 5: Day 65	Phone Call 5: Day 72	Visit 6: Day 84	Phone Call 6: Day 91
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographic data	X												
Medical history	X												
Prior and/or concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/Neurological exam	X			X		X		X		X		X	
Vital signs	X			X		X		X		X		X	
12-Lead ECG	X					X						X	
Urine pregnancy test (WOCBP)	X					X						X	
Serum Chemistry	X					X						X	
International RLS Rating Scale (IRLS Scale)		X		X		X		X		X		X	
Body weight and height		X		X		X		X		X		X	
Augmentation Severity Rating Scale	X	X		X		X		X		X		X	
Epworth Sleep Scale		X		X		X		X		X		X	
Hamilton Depression Scale		X		X		X		X		X		X	
MOS Sleep Scale		X		X		X		X		X		X	
Montreal Cognitive Assessment (MoCA)		X		X		X		X		X		X	
Fatigue Severity Scale		X		X		X		X		X		X	
Columbia-Suicide Severity Rating Scale (C-SSRS)		X		X		X		X		X		X	
Clinical Global Impressions (CGI)		X	X	X	X	X	X	X	X	X	X	X	X
Dispense 24-hour RLS Symptom diary	X							X					
Review of 24-hour RLS symptom diary		X		X		X		X		X		X	
Study drug dispensation		X						X					
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X

Investigational Product

Ecopipam (also known as PSYRX 101 or SCH 39166) hydrochloride is a potent, selective antagonist of human D1 and D5 dopamine receptors. Dopamine is a neurotransmitter in the central nervous system, and its receptors have been classified into two “families” based on their genetic structure: “D1” (including subtypes D1 and D5) and “D2” (including subtypes D2, D3 and D4). D1-receptor super-sensitivity may be a mechanism for the repetitive and compulsive self-injurious behaviors. Ecopipam is a selective antagonist of the D1-receptor family and had been investigated for the symptomatic relief of self-injurious behavior (SIB) in patients with Lesch-Nyhan Disease, Pathological Gambling and Tourette Syndrome. Detailed information about ecopipam development may be found in the Investigator Brochure.

Subjects will be randomized in a double-blind fashion to study drug: ecopipam or matching placebo, supplied by Psyadon Pharmaceutical for study period 1 and 2. Prior to drug dispensation to subjects, subjects will be provided a diary, instructed on daily morning dosing, and asked to return all unused drug and packaging with the diary to the clinic. Subjects will be instructed to report any concerns and/or side effects on contact calls that will occur between study visits.

The double-blind drug assignment code will be maintained in a confidential manner where investigator, study team and patients are unaware of individual treatment assignments. Randomization process must be completed by research personnel not involved in conduct of study visits. Only in the event of a subject related emergency with the specific request to unblind the study drug by the Principal Investigator will the identity of the double-blind drug will be disclosed.

Subjects will be seen six times to complete the study. Arm1 baseline/screening, Arm 1 week 3, Arm 1 week 5, Arm 2 baseline, Arm 2 week 3, Arm 2 week 5. Once daily morning dosing will occur for 5 weeks per arm with weekly dose escalation as the example shows below:

Study Period 1

- Ecopipam or matching placebo 25 mg by mouth for 7 days (week 1), followed by
- Ecopipam or matching placebo 50 mg by mouth for 7 days (week 2), followed by
- Ecopipam or matching placebo 100 mg by mouth for 23 days (weeks 3).
- Wash-out for 2 weeks to allow subjects to switch study arms.

Study Period 2

- Matching placebo or ecopipam 25 mg by mouth for 7 days (week 7), followed by
- Matching placebo or ecopipam 50 mg by mouth for 7 days (week 8), followed by
- Matching placebo or ecopipam 100 mg by mouth for 23 days (week 9).

Subjects will be allowed to reduce to a previous tolerated dose if needed. All other RLS medicines will remain stable.



IMP preparation blinding

Principal Investigator and study staff will handle the study drug and supplies in accordance with the protocol and GCP guidelines.

IMP receipt

1. Investigational drugs will be sent directly to Movement Disorders Clinic to the attention of the Principal Investigator. Upon receipt of IMP, the research staff will inventory these drugs at the time of receipt in the clinic to determine that they have been received in good condition and that the information on the packing slip matches exactly what has been sent. Any discrepancies will be promptly brought to the attention of the sponsor/supplier.
2. Principal Investigator (PI) will be notified of drug receipt. With knowledge of what is known about drug's toxicity, potency, sensitising potential and risk of cross-contamination, PI or delegate will visually inspect bulk IMP, verify its receipt in good condition and recommend packaging instructions per site SOP.
3. All appropriate follow-up required per drug sponsor will be completed.
4. All documentation accompanying or detailing the delivery are noted and filed in the Regulatory binder. This may include package inserts, certificates of compliance with GMP Guidelines, certificates of analysis (test products), or product release certificates (reference products). If any expected documents are missing, a designee must notify the Drug Sponsor without undue delay.
5. Drug will be stored in a temperature monitored locked cabinet in a limited access location.

IMP labeling

1. Study team member appropriately trained on GCP requirements and study protocol will complete IMP labelling
2. Another appropriately trained member of the team will review the labels before printing.
3. Label will include Kit ID, patient ID/randomization #/code, study drug name (i.e. PSYRX101 or matching placebo), dose, instructions on use and the following statement: "Caution: New Drug-Limited by Federal law to investigational use"
4. An unblinded study team member (or packager) is responsible for assigning computer generated randomization schedule to study patients.

5. Packaging area is appropriately cleaned, windows and doors closed, and extraneous materials removed.
6. Lot numbers and expiration dates will be verified before packing begins
7. The bulk IMP, required number of appropriately labelled containers, randomization list and IMP packing form/guideline are introduced into the packing area
 - a. Work with one type of IMP at a time. Bulk placebo IMP will be introduced into the packing area only after bulk IMP have been packed and unpacked (i.e. extra pills) have been accounted for.
8. Treatment dose units are packed per participant starting with the first participant number "RLS-001"
 - a. Dose units are selected from the bulk supply and transferred to the labelled containers according to computer generated randomisation list and protocol specific requirements
9. After all dosing units have been packed, packager must perform 3 point unit check to ensure packed IMP containers and labels have been correctly packed and correlate with randomization list
10. The packed IMP containers are securely stored in temperature monitored cabinet located in a restricted access storage area. Min/Max thermometer will be read and temperature recorded on a temperature log and thermometer reset will be performed at least once a day.
11. Documentation including unblinded treatment assignment (i.e. randomization code), #IMP unpacked and # IMP packed will be retained by packager and another back-up site personnel uninvolved with study procedures. Study site personnel will have access to randomization code in case of subject related emergencies.

IMP destruction

There are no plans to destroy left over investigational drug at site. After the study is completed, remaining drug will be returned to Psyaden Pharmaceuticals Inc for sponsor destruction.

Subject Sample

Rationale for Subject Selection and Sample Size Calculation

Patient Selection. Study subjects will be adult patients diagnosed with Restless Leg Syndrome and dopaminergic induced augmentation

Rationale for Sample Size Determination. Drug availability**Safety Monitoring of Subjects**

During the study, the Investigator and study team will be responsible for monitoring, collecting, following-up on, and reporting AEs and SAEs, as detailed in this section of the protocol. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) according to the definition below. Only adverse events associated with the research component of trial participation will be captured, examples include but are not limited to: somnolence, headache, insomnia.

The stopping rules for this trial will be determined by the Sponsor Investigator, Houston Methodist Hospital &/or Houston Methodist Research Institute, and/or HMRI Institutional Review Board. The Principal Investigator may withdraw a subject for their safety and welfare. Participants will be withdrawn at either 3x ULN for AST/ALT, kidney function changes from baseline as determined by BUN/Creatinine or when unintended pregnancy occurs.

Event Monitoring Definitions

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with use of any drug or medicinal product. AEs are to be reported to the IRB per IRB policy and to the sponsor at the time of annual reporting.

Serious Adverse Event (SAE): A serious adverse event (SAE) is any untoward medical occurrence that occurs irrespective of study treatment assignment, if it satisfies any of these criteria: results in death; is life-threatening; requires inpatient hospitalization or prolongs existing hospitalization; results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions; or if the event is a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. SAEs are to be reported to the IRB per IRB policy and to the sponsor at the time of IRB reporting for further reporting to the FDA.

Assessment of Intensity: The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each AE and SAE recorded in the subject record should be assigned to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

Relationship to Study Drug - Assessment of Causality: The Investigator is obligated to assess the relationship between study drug and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will assess causality based on the following definitions:

- Not Related (the AE was more likely explained by causes other than the study treatment).
- Related (the study treatment and AE were closely related in time and the AE may be explained by exposure to study product: e.g., known pharmacological effect or recurrence on re-challenge).

Participant Compensation

Participating subjects will not be provided compensation for their time and trouble. Study visits and/or study procedures only needed for the research study will be covered by the Sponsor-Investigator.

Compliance Statement

The Treatment of RLS Augmentation with Ecopipam, a D1 Specific Antagonist will be conducted in compliance with the IRB approved protocol, ICH-Good Clinical Practice (E6), applicable regulatory and institutional requirements.

Data Management and Storage

Data will be managed and stored using the Houston Methodist Hospital electronic medical record, questionnaires, and data collection forms, as needed. The data will be available only to the PI and authorized Study Team members.

Reporting of Study Findings

Study findings will be reported following regulatory guidelines and institutional policy in this regard.

References

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Attachments:

1. Informed Consent Document
2. Subject Diary
3. Clinical Global Impression
4. International RLS Rating Scale
5. Augmentation Severity Rating Scale
6. Epworth Sleep Scale
7. Hamilton Depression Scale
8. MOS Sleep Scale
9. Fatigue Severity Scale
10. Columbia Suicide Assessment scale
11. Montreal Cognitive Assessment