

Standardizing Care for Neuropsychiatric Symptoms and Quality of Life in Dementia (StaN)

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OBJECTIVES:

- propose adopting an algorithmic approach to non-pharmacological interventions, **psychotropics** use, combined with **standardized assessments**, non-pharmacological interventions, and measurement-based decision making referred to as the **Integrated Care Pathway (ICP)**.

REASONS FOR Integrated Care Pathway:

- Problem of polypharmacy
- Problem of suboptimal dosing
- Problem of variation
- Problem of absent non-pharmacological interventions

- Algorithmic treatment for mental disorders is known to result in better outcomes.
- key component is sequential approach to prescribing medications, thereby allowing for the target dose, and an appropriate duration of treatment at the target dose.

Groundwork for INTEGRATED CARE PATHWAY

- ICP is based on previous work done at CAMH (CENTRE FOR ADDICTIONS AND MENTAL HEALTH) to evaluate the feasibility and generate pilot data for an ICP approach to treat AD-AA.
- Preliminary data (CAMH): 45 patients with AD-AA.
 - 3 patients (6%) exited the ICP before completion
 - 42 patients completed the ICP successfully
 - 25 patients completed the CMAI-frequency scale
 - PRIMARY OUTCOME MEASURE: total score decreased from 57.5 (SD = 24.5) at baseline to 42.2 (SD = 18.4) at exit from the ICP ($t(24) = 3.59, p = 0.001, \text{Cohen's } d = 0.74$).
 - SECONDARY OUTCOME MEASURE: proportion of participants on polypharmacy. Only 1/42 patients exited the ICP on polypharmacy (2.4%) as compared to rates of up to 50% in the literature



DESIGN

- Design features
- PARTICIPANTS- SITES, SAMPLE SIZE
- Organization
- Visit schedule

STUDY DESIGN

- 1) Project initiation phase of 6 months (project months: 1-6)
- 2) Enroll and randomize 220 participants with AD-AA (110 inpatient and 110 in LTCFs) to ICP vs.TAU.
 - In this RCT phase of the project, participants will be treated for 12 weeks. (project months: 7-24). RCT WILL be completed by 18 months
- 3) During the last part of this project (project months: 25-36), we will analyze the data from the RCT and complete all naturalistic follow-ups. .

Sites:

- 7 sites across two settings:
- Inpatient (CAMH in Toronto, Douglas Hospital Research Centre in Montreal, Parkwood Institute in London and victoria hospital and the University of Calgary in Calgary)
- loNG TERM CARE fACILITIES (ltcf) affiliated with CAMH in Toronto and Parkwood Institute in London (Dearness Home and McCormick Home).
- 220 participants with AD-AA (110 inpatient and 110 in LTCHs) to ICP vs. TAU.

SAMPLE SIZE AND POWER:

- During the 18-month RCT phase of the study, plan to recruit and enroll 2-3 participants/month with AD-AA at each of the 7 sites (4 inpatient units and 3 LTCFs) over 15 months for a total of 110 randomized participants per setting (Inpatient and LTCFs)

Power Analysis for Hypothesis 1a (Effect on AD-AA) (N = 110/setting, $\alpha = 0.05$)		
Drop in CMAI-frequency in ICP at the end of study (vs. 5.0 points drop TAU)	Cohen's d	Power
20	0.81	98%
15.3 (as per pilot data)	0.56	80%
10	0.27	28%

ELIGIBILITY CRITERIA:

- **INCLUSION CRITERIA**

- A clinical diagnosis of Dementia of Alzheimer's or Mixed type
- AD-AA as defined by Agitation in cognitive disorders
- Participant or SDM able and willing to provide consent for enrollment in the study
- 50 years or older
- Medical stability to participate in the trial.

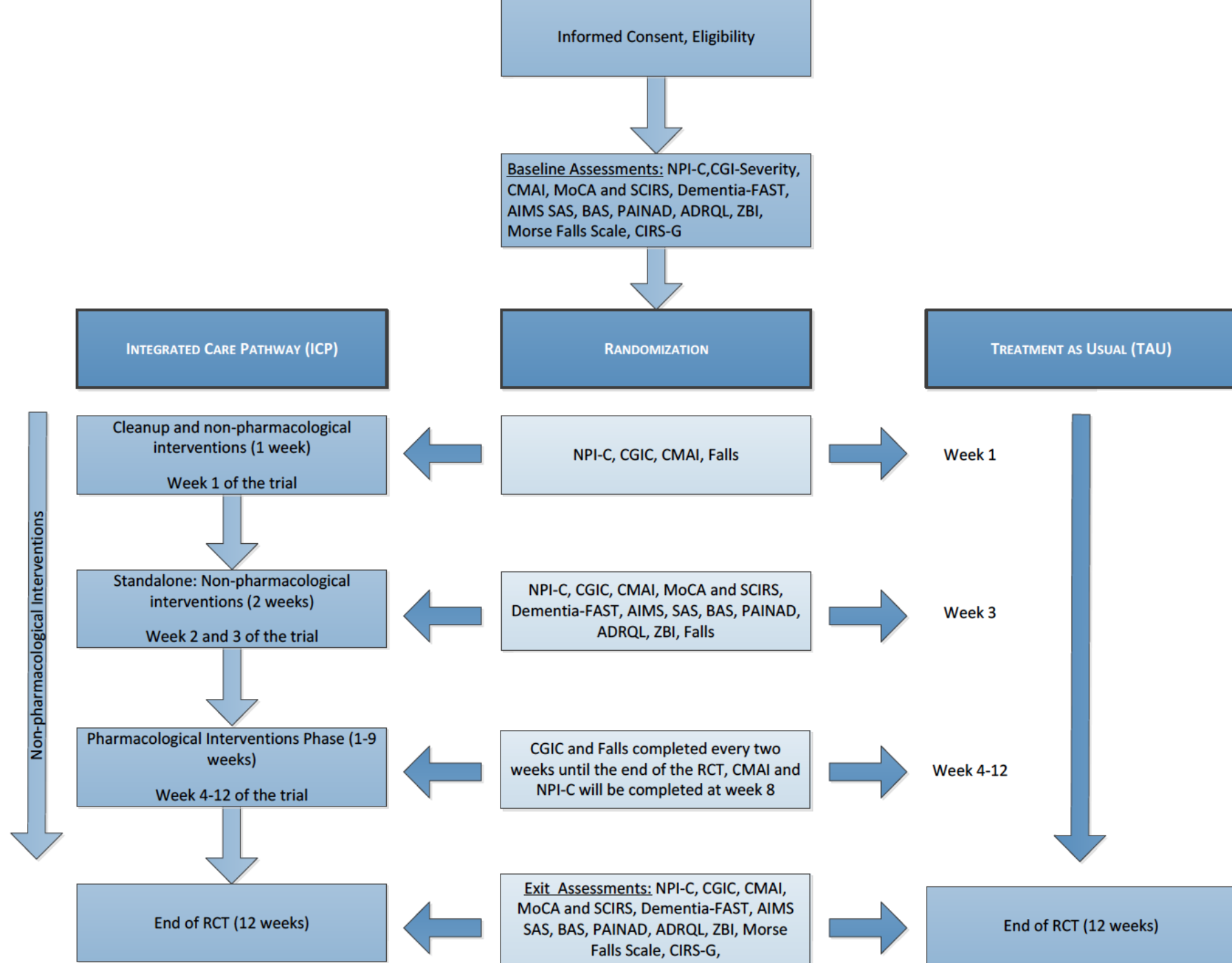
ELIGIBILITY CRITERIA:

- **EXCLUSION CRITERIA**

- Having dementia other than Alzheimer's or Vascular or Mixed type.
- DSM-5 diagnoses other than dementia that is thought to be significantly impacting the presentation of AD-AA such as delirium, bipolar disorder, or major depressive disorder.
- Any other reason which in the opinion of study investigator will make the study participation intolerable for the participant.

Outcome Measures:

- Primary:
 - Change in Cohen-Mansfield Agitation Inventory - Total Frequency Score (CMAI - Frequency)
 - baseline, 3 weeks, 8 weeks, and 12 weeks measures burden of agitation in patients with dementia. CMAI-frequency score ranges between 29 to 203, higher scores indicate worsening of symptom
 - Participants on Polypharmacy
 - baseline, 3 weeks, 8 weeks, and 12 weeks - percentage and total number of participants on 2 or more psychotropics
- Secondary:
 - The impact of the ICP on falls
 - Every 2 weeks- Recording the number of fall



Clinical Global Impression of Change

Global improvement: Rate total improvement whether or not, in your judgment, it is due entirely to treatment.

Compared to your patient's condition at time of first assessment, how much has s/he changed?

0 = Not assessed

1 = Very much improved

2 = Much improved

3 = Minimally improved

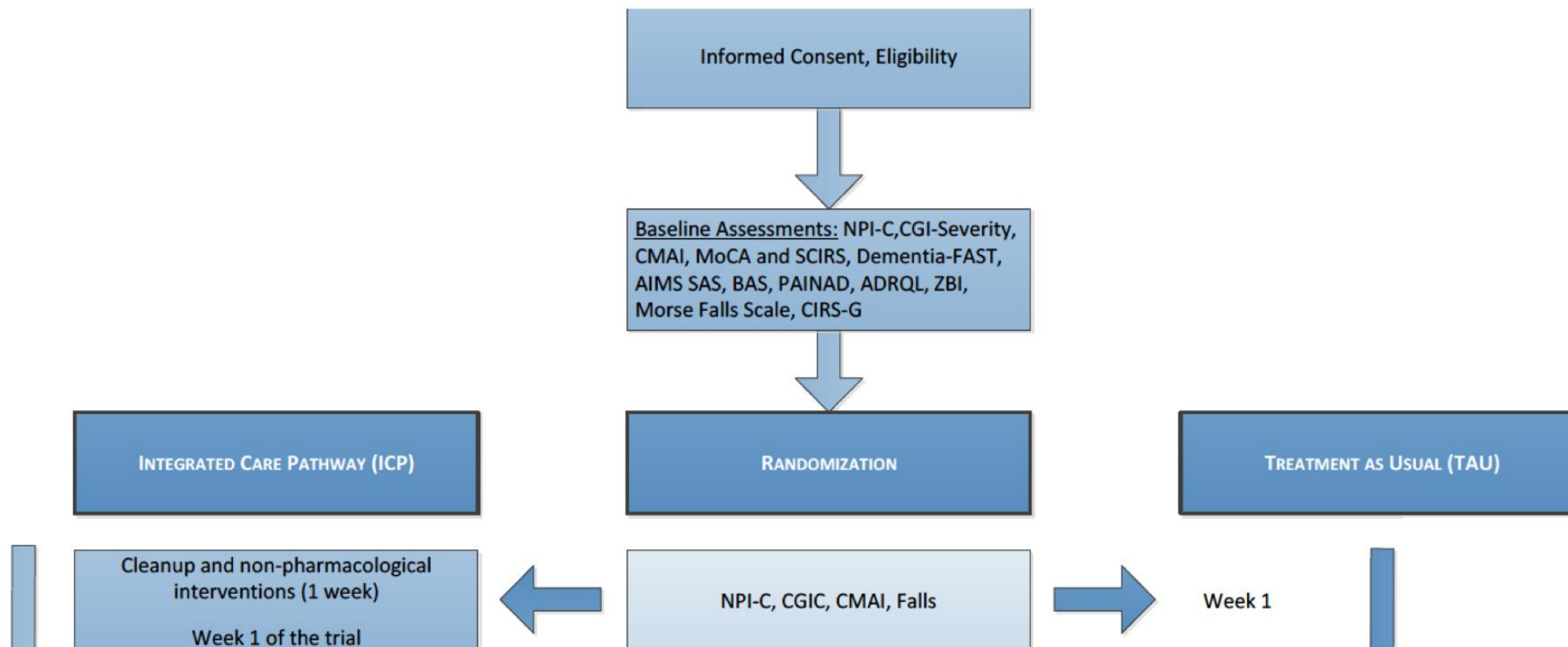
4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

BASELINE AND WEEK 1:

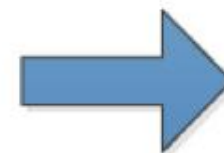
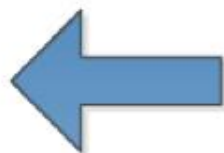


Standalone: Non-pharmacological interventions (2 weeks)

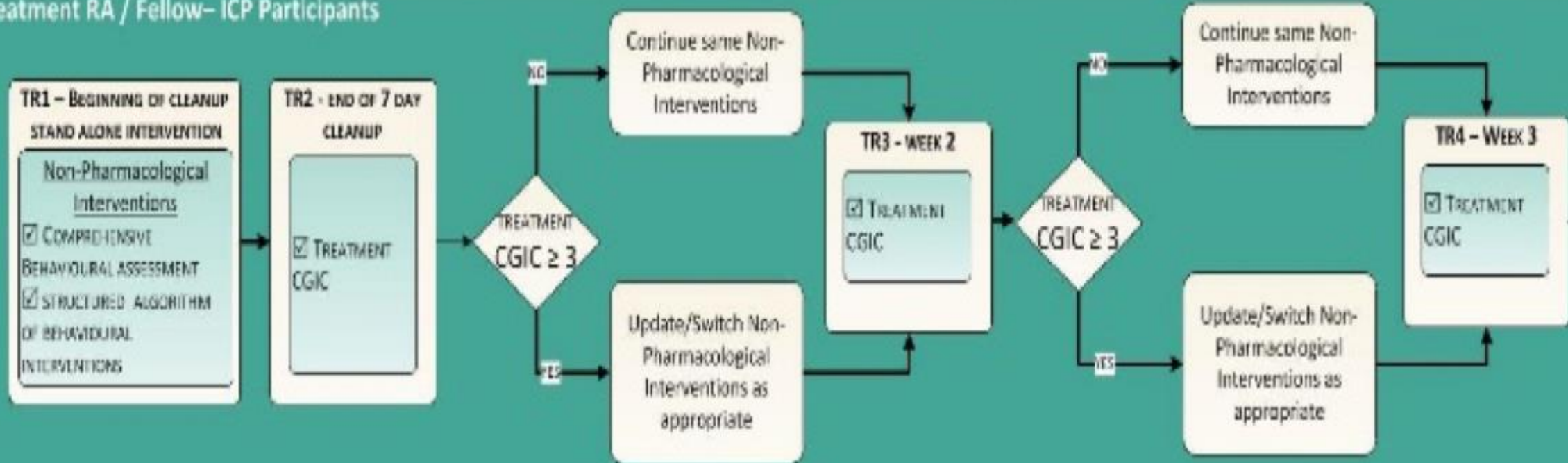
Week 2 and 3 of the trial

NPI-C, CGIC, CMAI, MoCA and SCIRS,
Dementia-FAST, AIMS, SAS, BAS, PAINAD,
ADRQL, ZBI, Falls

Week 3

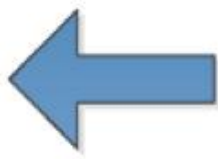


Treatment RA / Fellow- ICP Participants

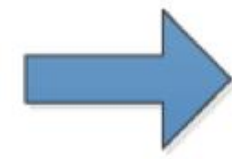


Pharmacological Interventions Phase (1-9 weeks)

Week 4-12 of the trial



CGIC and Falls completed every two weeks until the end of the RCT, CMAI and NPI-C will be completed at week 8



Week 4-12

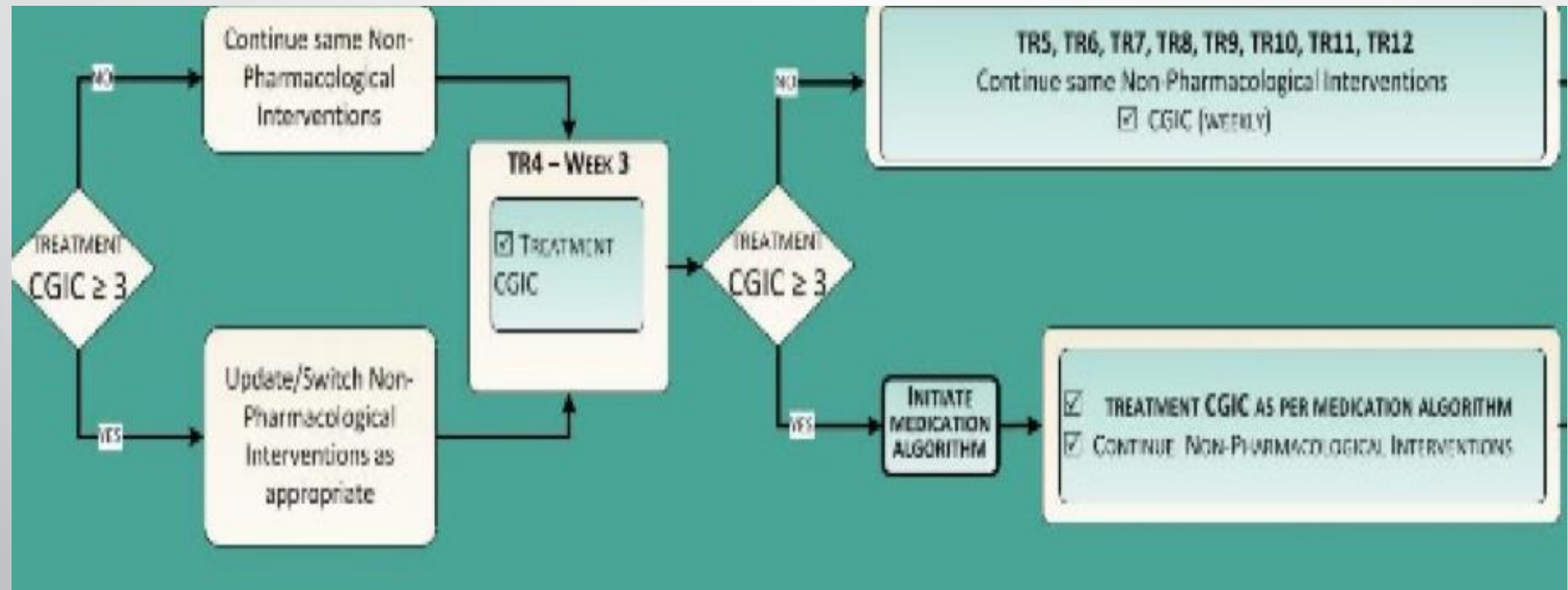
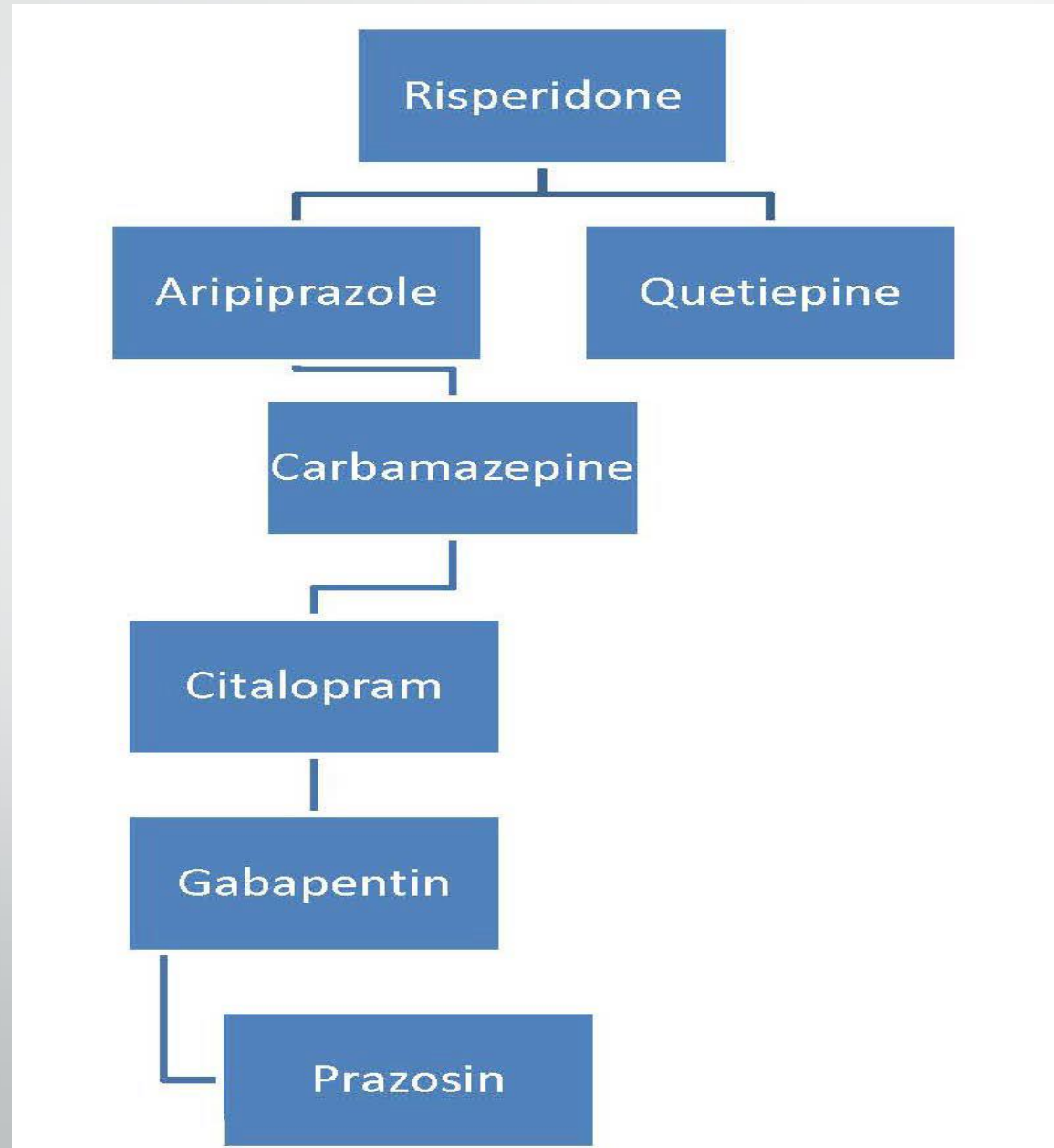


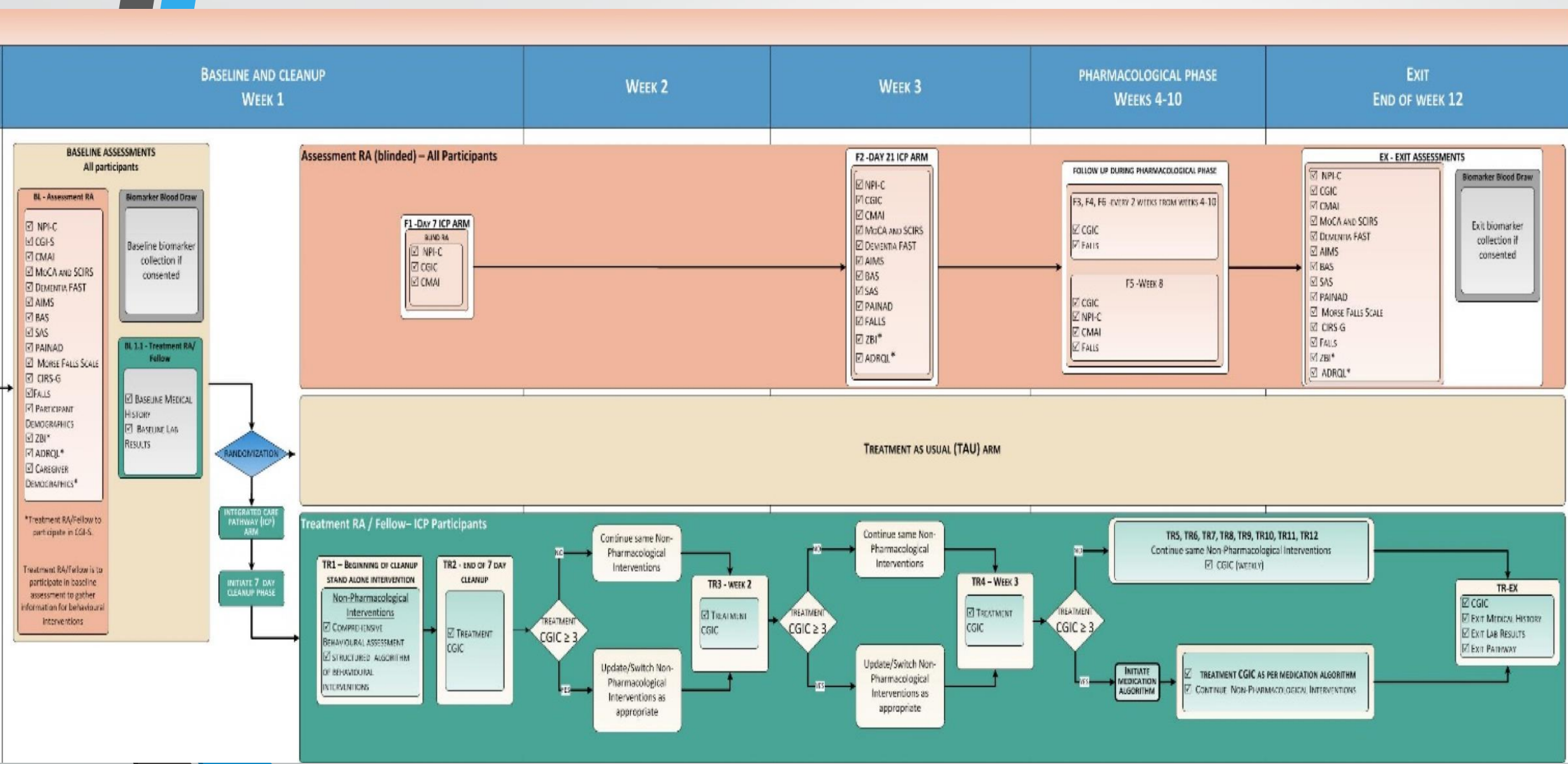
Figure 2: Medications Algorithm: Step-wise Progression.



LEVEL	DRUG	EVIDENCE
1	Risperidone	STRONGEST- Approved in Canada for symptomatic management
2A	Aripiprazole	WEAKER RCT evidence suggesting efficacy in psychosis associated with AD
2B	Quetiapine	WEAKER 6 RCTs reported a significant effect in reducing neuropsychiatric symptoms relative to placebo
3	Carbamazepine	1 successful RCT, CYP 3A4 inducer <u>Resistant or Unable to tolerate antipsychotics</u>
4	Citalopram	successful large RCT Max dose: 20 mg/day
5	Gabapentin	Case series & reports – mainly for sexual disinhibition
6	Prazosin	one small RCT- significant evidence (at 6mg /day)
7	Combination of ANY 2 (Partial Response)	

	DAY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
1	Risperidone single evening dose	0.5	0.5	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Risperidone (FRAIL) single evening dose	0.25	0.25	0.25	0.25	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
2a	Aripiprazole single evening dose	2.5	2.5	5	5	7.5	7.5	10	10	10	10	10	10	10	10	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
	Aripiprazole (FRAIL) single evening dose	1	1	2.5	2.5	2.5	2.5	5	5	5	5	7.5	7.5	7.5	7.5	7.5	10	10	10	10	10	10	10	10
2b	Quetiapine* divided doses (i.e. Start at 12.5mg b.i.d.)	25	25	50	50	75	75	100	100	100	100	100	100	100	100	150	150	150	200	200	200	200	200	200
	Quetiapine* (FRAIL) divided doses	12.5	12.5	25	25	37.5	37.5	50	50	50	50	50	50	50	50	75	75	75	100	100	100	100	100	100
3	Carbamazepine always b.i.d. (i.e. Start at 50mg b.i.d.)	100	100	100	100	200	200	200	200	300	300	300	300	300	300	300	400	400	400	400	400	400	400	400
	Carbamazepine (FRAIL) always b.i.d.	50	50	50	50	100	100	100	100	150	150	150	150	150	150	150	200	200	200	200	200	200	200	200
4	Citalopram single morning dose	10	10	10	10	10	10	10	10	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
	Citalopram (FRAIL) single morning dose	5	5	5	5	10	10	10	10	10	10	10	15	15	15	15	15	20	20	20	20	20	20	20
5	Gabapentin † ¶ divided doses (i.e. Start 100mg b.i.d.)	200	200	400	400	600	600	900	900	900	900	900	900	900	900	1200	1200	1500	1500	1800	1800	1800	1800	1800
6	Prazosin ¶¶ first dose = 0.5mg at bedtime, divided into b.i.d. thereafter	0.5	1	1	2	2	2	3	3	3	4	4	4	4	4	4	5	5	6	6	6	6	6	6
7 a	Combination Rx (based on drugs yielding partial response) or 7b GO TO ECT																							
	All doses are TOTAL daily dose in milligrams (mg) and where necessary should be divided as indicated. Decision points denoted by orange and red shading																							
	DAY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
	* divide Quetiapine daily dose into two equal doses, except in FRAIL regimen at 12.5mg/day and 37.5 mg/day. At 12.5mg/day give in evening only, at 37.5mg/day split as 12.5 mg / 25 mg																							
	† divide Gabapentin daily dose into two equal doses, except at 900 mg/day split as 400 mg / 500 mg, and at 1500 mg/day split as 700 mg / 800 mg																							
	¶ In patients with renal impairment gabapentin doses should be reduced according to renal function																							
	¶¶ In patients with hepatic or renal impairment, those using antihypertensives or those who are frail, titration should proceed more slowly																							
	EXTENSIONS																							
	DAY	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
	Risperidone single evening dose	1.5	1.5	1.5	1.5	1.5	1.5	1.5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	Risperidone (FRAIL) single evening dose	0.75	0.75	0.75	0.75	0.75	0.75	0.75	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Quetiapine divided doses (i.e. Start at 125mg b.i.d.)	250	250	250	250	250	250	250	250	300	300	300	300	300	300	300	300	300	300	300	300	300	300	
	Quetiapine (frail) divided doses	125	125	125	125	125	125	125	125	150	150	150	150	150	150	150	150	150	150	150	150	150	150	
	DAY	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	

Figure 2A: Medications Algorithm. Boxes shaded in blue are decision points for change of dose, termination of trial, or continuation of current dose; boxes shaded in orange are special decision points where 21 Day Extension of trial is possible for some medications. Decisions at decision points are guided by the Treatment-CGIC as described in the main text and performed by the treatment team for the ICP arm participants at the decision time points (shaded boxes). FRAIL - A dosing schedule involving lower doses is recommended where the patient is 'frail'. The need to consider a patient as 'frail' will be established by consideration of a) BMI/weight b) vital signs and c) mobility

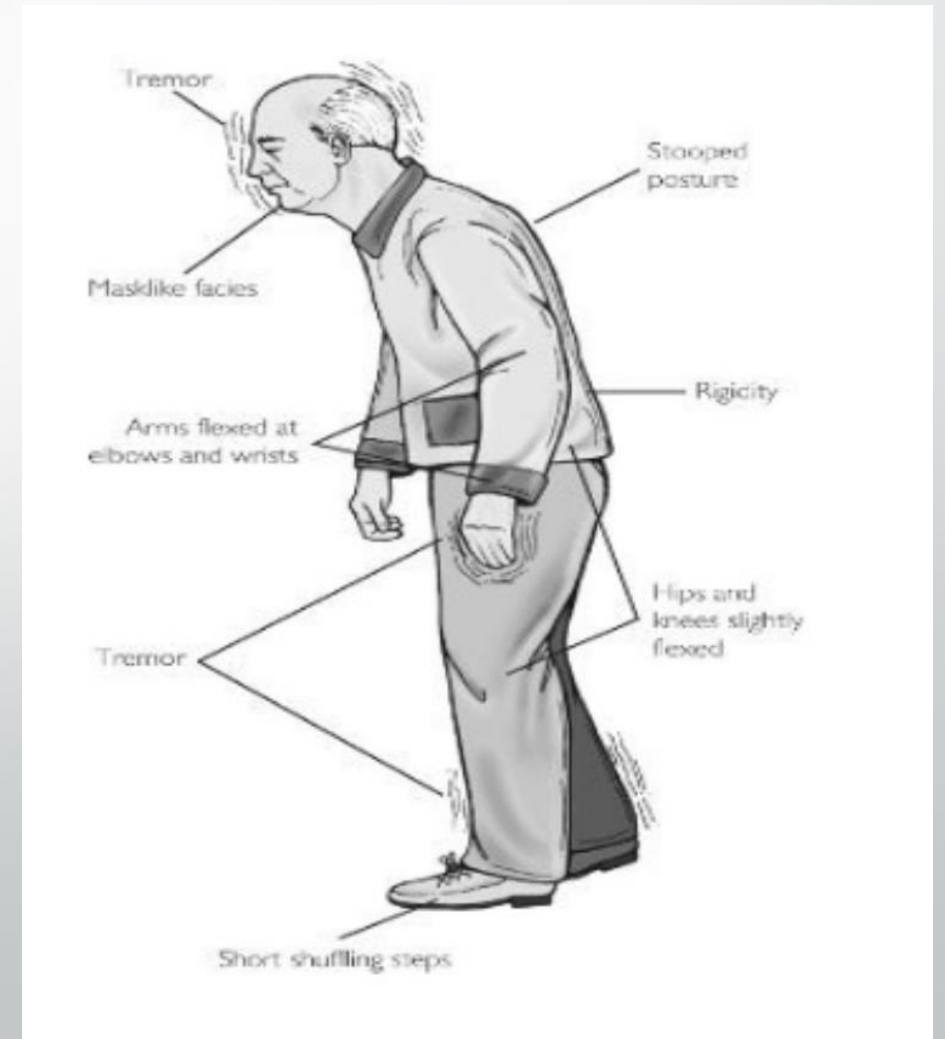


ASSESSMENT TOOLS:

Assessment Tools	Measures
Cohen-Mansfield Agitation Inventory (CMAI) (89)	Physical and Verbal AD-AA
Neuropsychiatric Inventory-Clinician (NPI-C) (15)	Delusions; Hallucinations; Dysphoria; Anxiety; Agitation/Aggression; Euphoria; Disinhibition; Irritability/liability; Apathy; Aberrant motor activity
Montreal Cognitive Assessment (MoCA) (90)	Attention/Concentration; Orientation; Executive functions; Memory; Language; Visuoconstructional skills.
Severe Cognitive Impairment Rating Scale (SCIRS) (91)	SCIRS will be administered if MoCA score is less than 5
Clinical Global Impression (CGI-S) (16)	Symptom severity at baseline
Modified Clinical Global Impression of Change (CGIC) (17, 18)	Treatment response
Abnormal Involuntary Movement Scale (AIMS) (92)	Tardive dyskinesia
Simpson-Angus Scale (SAS) (93)	Medication- induced parkinsonism
Barnes Akathisia Scale (BAS) (94)	Medication-induced akathisia
Pain Assessment in Advanced Dementia Scale (PAINAD)(95)	Severity of pain and impact of pain on daily functions
Dementia - Functional Assessment Staging Tool (FAST) (96)	FAST is a functional scale designed to evaluate the stage of dementia
Zarit Burden Interview (ZBI)(97)	ZBI assesses caregiver burden
Alzheimer Disease Related Quality of Life (ADRQL) (87)	Quality of life
Cumulative Illness Rating Scale for Geriatrics (CIRS-G)(98)	Measures the chronic medical illness burden

Adverse reactions of ANTIPSYCHOTICS:

- movement DISORDERS
 - PARKINSONISM
 - AKATHISIA
 - Tardive dyskinesia



SIMPSON ANGUS SCALE- parkinsonism

- 1. Gait:** The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:
 - 0 Normal
 - 1 Diminution in swing while the patient is walking
 - 2 Marked diminution in swing with obvious rigidity in the arm
 - 3 Stiff gait with arms held rigidly before the abdomen
 - 4 Stooped shuffling gait with propulsion and retropulsion
- 2. Arm Dropping:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:
 - 0 Normal, free fall with loud slap and rebound
 - 1 Fall slowed slightly with less audible contact and little rebound
 - 2 Fall slowed, no rebound
 - 3 Marked slowing, no slap at all
 - 4 Arms fall as though against resistance; as though through glue
- 3. Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
 - 0 Normal
 - 1 Slight stiffness and resistance
 - 2 Moderate stiffness and resistance
 - 3 Marked rigidity with difficulty in passive movement
 - 4 Extreme stiffness and rigidity with almost a frozen shoulder
- 4. Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)
 - 0 Normal
 - 1 Slight stiffness and resistance
 - 2 Moderate stiffness and resistance
 - 3 Marked rigidity with difficulty in passive movement
 - 4 Extreme stiffness and rigidity with almost a frozen elbow
- 5. Wrist Rigidity or Fixation of Position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:
 - 0 Normal
 - 1 Slight stiffness and resistance
 - 2 Moderate stiffness and resistance
 - 3 Marked rigidity with difficulty in passive movement
 - 4 Extreme stiffness and rigidity with almost frozen wrist

SIMPSON ANGUS SCALE- parkinsonism

6. **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:

- 0 The legs swing freely
- 1 Slight diminution in the swing of the legs
- 2 Moderate resistance to swing
- 3 Marked resistance and damping of swing
- 4 Complete absence of swing

7. **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:

- 0 The head falls completely with a good thump as it hits the table
- 1 Slight slowing in fall, mainly noted by lack of slap as head meets the table
- 2 Moderate slowing in the fall quite noticeable to the eye
- 3 Head falls stiffly and slowly
- 4 Head does not reach the examining table

8. **Glabella Tap:** Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

- 0 0-5 blinks
- 1 6-10 blinks
- 2 11-15 blinks
- 3 16-20 blinks
- 4 21 and more blinks

9. **Tremor:** Patient is observed walking into examining room and is then reexamined for this item:

- 0 Normal
- 1 Mild finger tremor, obvious to sight and touch
- 2 Tremor of hand or arm occurring spasmodically
- 3 Persistent tremor of one or more limbs
- 4 Whole body tremor

10. **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

- 0 Normal
- 1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
- 2 When excess salivation is present and might occasionally result in difficulty speaking
- 3 Speaking with difficulty because of excess salivation
- 4 Frank drooling

Barnes Akathisia Rating Scale (BARS)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

- 0 Normal, occasional fidgety movements of the limbs
- 1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
- 2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
- 3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

- 0 Absence of inner restlessness
- 1 Non-specific sense of inner restlessness
- 2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
- 3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness

- 0 No distress
- 1 Mild
- 2 Moderate
- 3 Severe

Global Clinical Assessment of Akathisia

- 0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
- 1 *Questionable.* Non-specific inner tension and fidgety movements
- 2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
- 3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
- 4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
- 5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.



B

B. Akathisia—continuous restlessness, inability to sit still. Constant moving, foot tapping, hand movements may be seen.



THANK YOU