Digital Therapeutics (DTx) for Alzheimer's Disease, Dementia and Mild Cognitive Impairment: A Pragmatic Review of Clinical Evidence

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BACKGROUND

A new form of non-pharmacological therapy known as "digital therapeutics" uses trained software programs to deliver evidence-based therapeutic interventions to patients to prevent, manage, or treat medical diseases. The FDA has granted Breakthrough Device Designation to Cognito's investigational device for the treatment of cognitive and functional symptoms associated with mild-to-moderate Alzheimer's Disease. [1] . The major challenge for all DTx manufacturers is to produce robust clinical evidence that will have a sufficient impact on their benefit-risk assessment to justify market approval and subsequent necessary reimbursement decisions. The FDA guidelines 21 CFR 601.41 for approval specify that the endpoint must be based on epidemiological, therapeutic, or pathophysiologic to gauge clinical benefit rather than just affect survival or irreversible morbidity. [2] Outcomes for AD-Dementia proposed by European regulations mandate evaluation of clinical benefit in three domains assessed by tests: cognition, functional activities of daily living, and holistic clinical response that captures quality of life and clinician evaluation as reflected by global assessment.

OBJECTIVE

This review focuses on clinical evaluation endpoints used by DTx manufacturers for Alzheimer's Disease, Dementia and Mild Cognitive Impairment indications to demonstrate efficacy across the domains of cognitive, functional, and overall benefit.

METHODOLOGY

A pragmatic literature search was conducted in Google Scholar, Clinicaltrials.gov, and PubMed; using search terms for: Digital Therapeutics/Digital Health Interventions, Alzheimer's Disease, Dementia, and Mild Cognitive Impairment. Inclusion criteria were then applied to the search- (i) Digital therapeutics/interventions aimed at managing/treating/slowing the progression of AD, (ii) clinical studies conducted by the DTx to prove efficacy and safety endpoints. Exclusion criteria for the selection of the articles for review were – (i) Digital health interventions aimed at monitoring only (ii) observational reports without clinical endpoints quantified (iii) Letters, comments, reviews, and qualitative studies. The information was then extracted in PICOS format and qualitatively analyzed using a thematic approach.

RESULTS

7 DTx interventions were included for analysis. The label indications reported were: Alzheimer's Disease (n=5), Dementia (n=4), Mild Cognitive Impairment (MCI) (n=5), and Subjective Cognitive Decline (n=2).

RCT No.	Name of Digital Therapeutic	Type of intervention	Description	Indications
NCT04559789	MindMate+	Behavioral intervention	Health coaching and lifestyle intervention to reduce/delay cognitive decline	· Alzheimer's Disease · Dementia · MCI · Cognitive decline
CT [3]	Brain+	Cognitive stimulation Therapy	Enhance cognitive function	· Dementia
NCT04897464	B-Gaze Therapy Alzheimer	Cognitive Training	Improve eye motion control thus improving cognitive processing of visual information	· Alzheimer's Disease · MCI
NCT04240665	Digital Memory Notebook (DMN)	Cognitive Training	Improve daily function, supportive care	· Alzheimer's Disease · MCI · Cognitive Decline
NCT05637801	Cognito Therapeutics – Sensory Stimulation System (GS120)	Gamma Sensory Stimulation	Slow down disease progression	· Alzheimer's Disease · Dementia · MCI
NCT05059353	NeuroGlee	Reminiscence therapy	Cognitive training improves Cognition and quality of life	· MCI
NCT04570215	Gotcha!	Speech and Language Therapy (SALT)	Improve naming performance on trained items, attention span, social activity and participation, and overall wellbeing.	· Alzheimer's Disease · Dementia · Anomia

Type of intervention	Cognitive Endpoints	Functional Endpoints	Other Endpoints
Cognitive Training (n=2)	· Adenbrooke Cognitive Examination · Mini-Mental State Examination (MMSE) · Neuropsychological test battery (NTB) · Composite Cognitive Score		
Cognitive stimulation Therapy (n=1)	· Mini-Mental State Examination (MMSE)	ADL - Activities of Daily Life	· Cohen-Mansfield Agitation Inventory (CMAI) scale · Cornell Scale for Depression · Dementia Observation System (DOS) scale · QoL-AD
Reminiscence therapy (n=1)	· Neuropsychological test battery (NTB	Caregiver Questionn aire (CQ).	· State subtest of the State/Trait Anxiety Inventory (STAI), Emotional thermometer ET, Neuro-QoL Depression Scale-Modified
Gamma Sensory Stimulation (n=1)	· Cognitive Training	Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)	· Clinical Dementia Rating- Sum of Boxes (CDR-SB)
Cognito Therapeutics – Sensory Stimulation System (GS120)	· Mini-Mental State Examination (MMSE)		
Speech and Language Therapy (SALT) (n=1)	· Participant and/or Caregiver Reported Outcome Measures (PROMS)		· Computer-based assessment of choice reaction time (CRT)

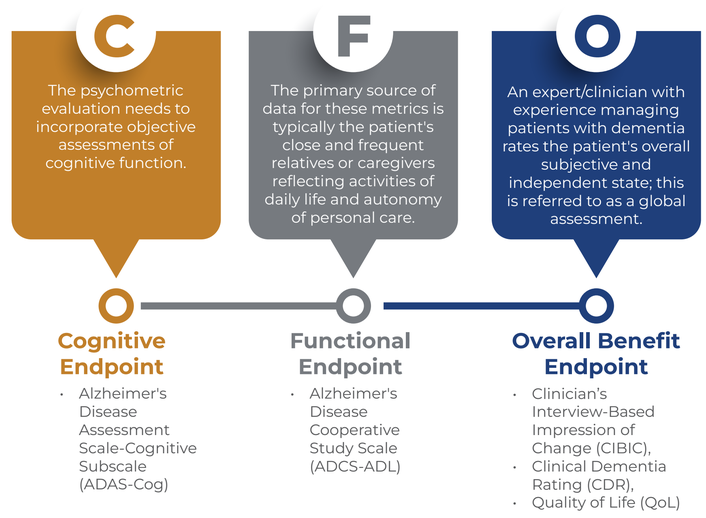
Except for the Mini-mental state examination (MMSE) and the neuropsychological test battery (NTB) there was no consistent use of scales to measure clinical endpoints for the same indications. Alzheimer's Disease Cooperative Study Scale (ADCS-ADL) was frequently used to assess fundamental and instrumental daily living tasks.

Cognitive Training DTx aimed at enhancing chronic illness self-management along with AD lifestyle and mood, and brain blood flow. The Gamma sensory stimulation measured radiographic analyses along with assessment of cognitive function. Other interventions based on cognitive stimulation and reminiscence captured mental health functions through the Neuro-QOL Depression Scale-Modified (NQOL) with a focus on quantifying QoL.

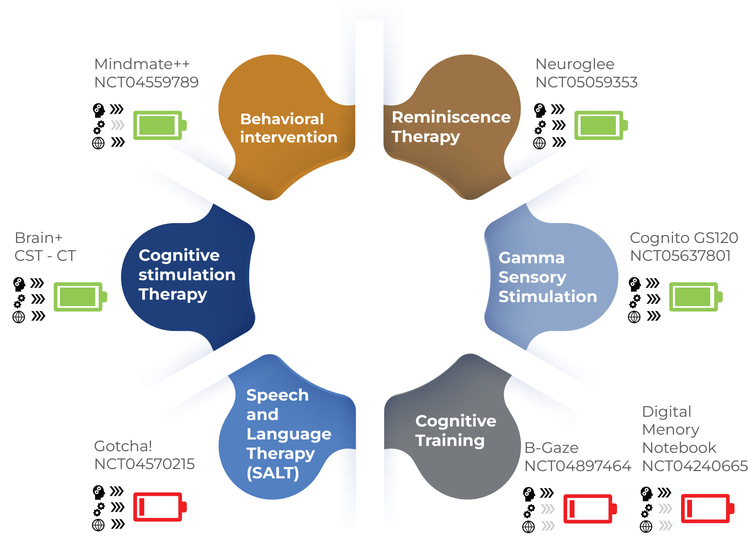
DISCUSSION

Regulators demand that measuring the efficacy of interventions in Alzheimer's disease, dementia, and mild cognitive impairment must use criteria to assess benefit across cognitive, functional, and overall benefit. Two crucial factors must be stated, one that evaluates the cognitive purpose [4] and the other therapeutic value of cognitive improvement. When this is achieved, the overall benefit (response) should be evaluated, and the effect of therapy should be portrayed as the proportion of patients who obtain a clinically significant benefit (response), laying the groundwork for compelling clinical evidence. At this point, how DTx will perform over the long term in terms of slowing progression and enhancing cognitive function is unknown as most of these DTx are in initial phases of development and none have been compared to pharmacotherapeutic including biological interventins.

Table 2. Domains of assessment for regulatory approval.



Evaluation of therapeutic efficacy on the basis of inclusion of endpoints from 3 domains : Cognitive, Functional and Over-all Clinical Response



REFERENCES

1. Cognito Therapeutics Receives FDA Breakthrough Device Designation for Next-Generation Digital Therapeutic in Alzheimer's Disease. (2021, January 12). Businesswire.Com.
2. 21 CFR 601.41 -- Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. (n.d.). Ecfr.Gov.
3. Results from a clinical study provide promising feasibility indications for Brain+' CCT technology for cognitive training. (n.d.) Cision.Com.
4. Broich, K. (2007). Outcome measures in clinical trials on medicinal products for the treatment of dementia: a European regulatory perspective. International Psychogeriatrics, 19(03), 509. doi:10.1017/s1041610207005273

CONCLUSION

Digital therapeutics offer a new approach to managing AD, with the potential to improve cognitive function, mood, and quality of life. These potential benefits must be captured using relevant and validated tools. More research is needed to evaluate the long-term efficacy and accessibility of DTx for AD, and ethical guidelines should be developed for their use. It will be important yet onerous to compare the outcomes of different DTx, and compare them to existing pharmacological / biological therapies.

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