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REVIEW

Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition

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ABSTRACT

Background: The International Psychogeriatric Association (IPA) published a provisional consensus definition of agitation in cognitive disorders in 2015. As proposed by the original work group, we summarize the use and validation of criteria in order to remove "provisional" from the definition.

Methods: This report summarizes information from the academic literature, research resources, clinical guidelines, expert surveys, and patient and family advocates on the experience of use of the IPA definition. The information was reviewed by a working group of topic experts to create a finalized definition.

Results: We present a final definition which closely resembles the provisional definition with modifications to address special circumstances. We also summarize the development of tools for diagnosis and assessment of agitation and propose strategies for dissemination and integration into precision diagnosis and agitation interventions.

Conclusion: The IPA definition of agitation captures a common and important entity that is recognized by many stakeholders. Dissemination of the definition will permit broader detection and can advance research and best practices for care of patients with agitation.

Key words: agitation, Alzheimer's disease, dementia, International Psychogeriatric Association, aggression, neuropsychiatric symptoms, Behavioral and Psychological Symptoms of Dementia

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Introduction

Agitation is a common and disabling aspect of many neurocognitive disorders including Alzheimer's disease (AD), non-AD types of dementia, and mild cognitive impairment (MCI) (Panca *et al.*, 2019; Halpern *et al.*, 2019; Van der Mussele *et al.*, 2015). In 2014–2015, the International Psychogeriatric Association (IPA) convened a group of international experts on dementia and agitation that led to the IPA Provisional Consensus Clinical and Research Definition of Agitation in Cognitive Disorders (Cummings *et al.*, 2015.). That work raised awareness and attention to both the clinical condition and the need to use a criteria-driven diagnosis to detect and treat this condition. As proposed in the original report, we summarize the experience of several years of utilization, acceptance by regulatory authorities to define trial populations, validation in clinical and research populations, and broad research application, to support the removal of the designation of "provisional." Here we report from the current IPA work group, describing the progress in our understanding of agitation, the IPA processes for revision (meetings, surveys, involvement of affiliated specialties), and the re-titled criteria. We first provide a summary of the current state of knowledge about agitation in cognitive disorders in terms of prevalence, cost, and underlying biology and the development of the provisional IPA criteria. Next, we describe the work to support the value of the IPA definition from provisional to finalizing these criteria will be described. We describe an array of venues and clinical circumstances in which agitation in cognitive disorders is observed. We involved patients and caregivers in the process of developing an acceptable and useful vocabulary to describe behaviors considered here as components of "agitation." We provide recommendations for implementation of the agitation in cognitive disorders criteria to maximize their usefulness in research and clinical care. We developed an algorithm with guidance for use of psychosocial and pharmacologic interventions for patients meeting the IPA criteria for agitation (Cummings, in review). Finally, we will describe the work to remove "provisional from the definition."

Current understanding of agitation.

Prevalence of agitation in cognitive disorders

Behavioral symptoms of dementia are recognized in the moderate to severe stages of disease but may actually occur throughout all stages. A study among nursing home patients reported presence of agitation between 26% and 33% at any point in time but cumulative and persistent agitation approached 60% (Selbaek *et al.*, 2014). In a study of 512 cases of MCI or dementia within a Memory Disorder Clinic, agitation was reported in 25% of those with MCI and 45% of those with dementia (Chan *et al.*, 2003). Using electronic health records identifying 320,886 cases with an AD or other dementia diagnosis, 44.6% had agitation with higher rates among those who could be classified as with moderate to severe dementia as compared to those who were could be classified as with mild to moderate dementia (Halpern *et al.*, 2019). In a study of home-dwelling research participants who had cognitive impairment ranging from mild to moderate/severe dementia, prevalence of agitation as defined by a clinician ranged from 8.3% to 48.9% (Sano *et al.*, 2022). Overall, these reports demonstrate the presence of agitation across the continuum of cognitive impairment with increasing prevalence with dementia severity.

Cost of agitation

It is important to recognize the economic consequences of agitation. Costa and colleagues found that across eight European countries, the increased cost of care for agitated compared to non-agitated people with dementia living at home was €445 per month, and for those living in long-term care facilities, the cost differential was €561 per month (2014 prices) (Costa *et al.*, 2018). The main driver of home care expenditures was the informal costs (73%); institutional care costs were the main driver in for those in long-term care (53%). A population study of all individuals with a diagnosis of AD and treated with mental health services in the Southeast London catchment area reported that agitation was associated with higher risk of admission to and days spent in care homes, mental health, and general hospitalization, as well as higher cost associated with any institutional admission in 6 months (Knapp *et al.*, 2016). Baseline data from 1424 residents with dementia living in care homes (part of Managing Agitation and Raising Quality of lifE in dementia (MARQUE) study) showed that a one-point increase in the CMAI was associated with a 0.5 percentage points increase in annual costs, with excess annual cost associated with agitation per resident with dementia estimated at £1125 (Panca *et al.*, 2019, Marston *et al.*, 2020). A study of 79 people with advanced dementia residing in 13 nursing homes in London and the southeast of England with Functional Assessment Staging Tool (FAST) grade 6e and above assessed participants every 4 weeks for a maximum of 9 months or death. Health and social care costs, and costs of providing informal care varied significantly by CMAI near the end of life, from £23,000 over a 1-year period with no agitation symptoms (CMAI agitation score 0–10)

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to £45,000 at the most severe level (CMAI agitation score > 100) (2012£) (Buylova Gola *et al.*, 2020). In the US, a cross-sectional analysis of the Aging, Demographics, and Memory Study (ADAMS) of individuals with cognitive impairment found that those with clinically significant agitation (defined as frequency score × severity score >4 using the NPI) received an excess of 20 hours of additional care per week in active help and supervision after adjusting for socio-demographics, cognitive category, and medical comorbidities (Okura & Langa 2011). Data from incident dementia cases from the Cache County Study on Memory in Aging (CCSMA) and their caregivers followed up semiannually for up to 10 years (2002–2012) showed that each point increase in the NPI-subdomain score of agitation/aggression was associated with a 7.6% increase in informal costs (Rattinger *et al.*, 2019). Another study using people with dementia in the ADAMS study found informant distress was related to psychosis or agitation but not the symptom burden and was associated with increased emergency department (ED) utilization, inpatient hospitalization, and Medicare expenditures (Maust *et al.*, 2017).

Neurobiological correlates of agitation

The expansion of technologies and neuropathological datasets provide opportunities to better understand brain and agitation-behavior relationships, especially within AD. Amyloid positron emission tomography (PET) is increasingly used to demonstrate which older individuals with normal cognition, MCI, and dementia have excessive brain amyloid and are within the AD continuum. Using this approach, Goukasian and colleagues found that in the AD Neuroimaging Initiative (ADNI), MCI patients with amyloid were more likely to exhibit agitation than those without, and the presence of agitation or the onset of new agitation in MCI with brain amyloid identified participants who progressed more rapidly to dementia than those without agitation (Goukasian *et al.*, 2019). Another study of participants in ADNI with normal cognition, MCI, and AD explored neural correlates of agitation, framed as mild behavioral impairment (MBI) impulse dyscontrol symptoms (Gill *et al.*, 2021). Agitation was associated with 1) lower fractional anisotropy and greater mean axial and radial diffusivity in the fornix, 2) less fractional anisotropy and greater radial diffusivity in the superior fronto-occipital fasciculus, 3) greater axial diffusivity in the cingulum, 4) greater axial and radial diffusivity in the uncinate fasciculus, and 5) gray matter atrophy, that is parahippocampal cortical thinning. These findings suggest that AD-related atrophy and changes in white matter integrity may identify those likely to exhibit agitation symptoms, even in advance of cognitive impairment. Similarly, a machine learning study of ADNI participants across the cognitive continuum explored neuroimaging and behavioral measures for classification and prognostic utility. In a three-class experiment to predict normal cognition, MCI, or AD at 40 months, both neuroimaging and behavioral features were required. Of the seven features needed, four were structural (left hippocampal volume, left entorhinal thickness, left entorhinal volume, left middle temporal gyrus thickness), and three were behavioral (MBI total score, impulse dyscontrol score, and emotional dysregulation score) (Gill *et al.*, 2020). These findings further support agitation as a salient component of dementia, potentially manifesting in advance of dementia, and necessitating research to further identify neural correlates and potential treatments.

Using fluorodeoxyglucose (FDG) PET, Weissberger and colleagues showed that in patients with mild to moderate AD, those with agitation had reduced glucose metabolism in the right temporal, right frontal, and bilateral cingulate cortex compared to those without agitation (Weissberger *et al.*, 2017).

Autopsy studies demonstrated that reported agitation during life of AD patients was associated with Braak stage I/II and Braak stage III/IV based on the distribution of neurofibrillary tangles in the brain at time of death (Ehrenberg *et al.*, 2018). Sennik *et al.* (2017) studied agitation in a cohort of patients with neuropathologically confirmed AD using the NACC database and found a positive association with severity of AD pathology and a negative association with vascular lesions of the brain (Sennik *et al.*, 2017). Smoking, TBI, and presence of TDP-43 were associated with the presence of agitation. Studies of cortical atrophy in AD using magnetic resonance imaging (MRI) document greater agitation in those with great posterior atrophy of the right hemisphere (Hsu *et al.*, 2017).

Finally, Ruthirakuhan *et al.* investigated the relationship of plasma biomarkers to response to treatment of agitation with nabilone in patients with AD (Ruthirakuhan *et al.*, 2020). They found that decreased agitation following treatment with nabilone was associated with decreased level of tumor necrosis factor (TNF-α), a marker of inflammation.

Taken together, these studies illustrate the breadth of potential mechanisms playing a role in agitation in populations with multiple pathologies, supporting the current approach to create a definition across the spectrum of cognitive impairment. Further work may lead to a wider range of biological targets for interventions to address this debilitating condition.

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Development of the IPA agitation criteria

In 2014–2015, the IPA convened a group of international experts on dementia and agitation, conducted two surveys, and engaged in a iterative process that led to the IPA Provisional Consensus Clinical and Research Definition of Agitation in Cognitive Disorders (Cummings *et al.*, 2015). The consensus yielded four criteria, as follows: 1) patients meet criteria for cognitive impairment or dementia syndrome, 2) patients exhibited verbal or motoric behaviors persistently or frequently recurring (i.e. for a period of 2 weeks or more) that caused distress, 3) behaviors produced excess disability, and 4) behaviors were not solely attributable to another psychiatric, medical, or environmental condition. These criteria reflected the input of clinicians as well as researchers, who, through a rigorous and transparent consensus process created a definition for a serious condition that was readily recognized and acceptably standardized with clinical skills and widely available tools.

Application of the IPA agitation in cognitive disorders criteria since 2015

Overview

Since its publication, the IPA provisional criteria have been widely discussed and broadly utilized with careful consideration to operationalizing the criteria for use in research. The Agitation in Dementia Working Group (ADWG) review this work here to provide support for changing the title of the IPA criteria for agitation in cognitive disorders to remove the word "provisional" given its current acceptance and use in the field. We propose that the criteria are now standard in many types of research and can be regarded as accepted rather than transitional. The criteria have been used in observational studies and in non-pharmacologic and pharmacologic intervention trials, as well as in guidelines from professional societies and government agencies. We propose that the presence of the criteria raises awareness of the condition and improves the quality of the research. Its broad acceptance, described below, supports removal of "provisional" from the definition which will further support research and care efforts.

Citations in the literature

A literature review which included Google Scholar, EBSCO Host, and PubMed databases from 2015 to April 2021 was conducted to search for citation of use of the provisional consensus definition provided by the IPA (Cummings *et al.*, 2015). Keywords included agitation gerontology, agitation definition, agitation dementia, and similar terms. Results were narrowed to include only the IPA definition in the English language. A total of 53 articles were found that cite the Cummings *et al.*, 2015 article. One article referred to pre-clinical animal studies. The most common use of the provisional definition citation was in review articles and commentaries ($N = 24$), many of which stated that there is no clinical definition for agitation, but that the IPA definition provides one option to define agitation. A common theme was that the presence of the behaviors included in the criteria was assessed using many different instruments. Griffiths and colleagues cited the IPA consensus definition and noted that "there is still a need to refine and validate assessment tools to accurately evaluate agitation as a clinical outcome" (Griffiths *et al.*, 2020). Of the remaining citations, 15 were observational human studies; 8 were pharmacological trials, and 5 were non-pharmacologic trials. The literature review established that researchers are aware of the IPA definition and include the definition in their methods sections while using a variety of tools to operationalize the consensus definition. Instruments for assessing agitation differ, creating challenges for use of standardized measures across research and clinical venues. This challenge was the focus of a EU-US Task Force report in 2018 that made specific proposals for operationalizing the criteria including using existing tools that provide item banks from which to choose the most useful items and a specific recommendation to improve the accuracy of caregiver reports by better training and education of caregivers (Sano *et al.*, 2018).

Use of the criteria in professional societies and governmental guidelines

We also undertook an assessment of the use of the criteria by professional and governmental agencies. National-level Alzheimer or dementia care government or advocacy group guidelines published in English since 2015 were reviewed for use of the IPA provisional guidelines; none were found to include the IPA definition. Guidelines, even prior to 2015 guidelines seldom mention agitation although one report from Ireland refers to delirium, paired with agitation, in their documents (The Irish National Dementia Strategy, 2014). Publicly available professional association guidelines from twelve organizations were reviewed for use of the provisional definition; few guidelines talk about the behavioral and the specific agitation problems, and only one referenced the (Cummings *et al.*, 2015) article. List of professional associations reviewed are available upon request. Some guidelines discuss delirium or dementia but not linked with agitation.

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Use of the criteria in clinical trials

An examination of registered clinical trials for agitation in dementia was undertaken to evaluate the use of the IPA criteria. Given the lag between trial planning and final publication, trial results may not yet be in the literature and ClinicalTrials.gov; the largest clinical trials database maintained by the US National Library of Medicine at the National Institutes of Health (NIH), publicly available since February 2000, was examined for trials using the criteria. Key search terms included "dementia" and "agitation," trial start dates spanned between 01/01/2015 and 07/01/2021. The search identified 55 interventional clinical studies. Of the 55 trials, 31 assessed the efficacy/tolerability/safety of treatments for agitation in dementia, 24 did not address agitation and were thus excluded from analysis. Among the 31 agitation trials, 25 used specific criteria to define agitation in the study inclusion section, 6 did not. The criteria used included IPA provisional agitation criteria, or criteria that were defined by existing scales such as the NeuroPsychiatric Inventory (NPI) (Cummings *et al.*, 1994), and Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield & Billig 1986). Between 2015 and 2021, 16 of the 25 trials (64%) used IPA criteria, 7 (28%) used NPI, and 2 (8%) used CMAI (Figure 1). The 16 trials using the IPA criteria involved 9 investigational agents with a variety of mechanisms of action including antidepressants, antipsychotics, cannabinoids, adrenergic receptor modulators, and dextromethorphan. Among those studies, 12 were phase III trials and 4 were phase II trials. Since 2020, all eight agitation trials conducted used the specific IPA definition for agitation as part of the study entry requirement. In contrast, among the seven trials conducted in 2018 and nine in 2017, only three (43%) and eight (89%) trials used the specific criteria, respectively. Since the introduction of IPA agitation criteria in 2015, they have been used more often than any other agitation criteria in clinical trials. In 2020 and 2021, 75% used the IPA criteria.

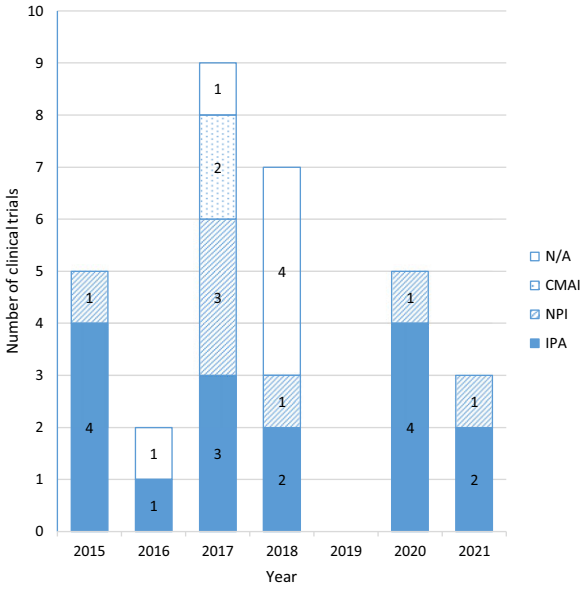

Figure 1. Number of clinical trials by year which used specific criteria to define agitation (01/01/2015 to 07/01/2021).

Evaluating the criteria in clinical populations

The IPA criteria were also examined in a well-characterized cohort of community-dwelling older adults with a range of cognitive impairment using data from 19,424 individuals enrolled in the National Alzheimer Coordinating Center Unified Data Set (NACC-UDS) (Sano *et al.*, 2022). The clinician's diagnosis of agitation was used as a gold standard in those with MCI and dementia. A "scale-based definition" was also created. For this, behavioral status was assessed using items from the Neuropsychiatric Inventory–Questionnaire (NPI-Q) to define agitation symptoms and standardized assessments of function (including the Functional Assessment Scale and Clinical Dementia Rating Scale Sum of Boxes) assessed "excess disability." Patterns of psychiatric comorbidities were examined to determine if they were consistent with IPA criterion D. Despite the fact that individuals were part of a research project that required significant engagement, making it unlikely that they were experiencing active behavioral disturbances, agitation prevalence ranged from 15 and 48% depending on the severity of cognitive impairment and the definition applied. There was agreement between the selected NPI-Q measure of agitation and clinician judgment with sensitivity = 0.79 and specificity = 0.69. More than 84% of those with clinician judgment of agitation and 74% of those meeting the scale-based definition of agitation demonstrated excess social/functional disability. The pattern of comorbid psychiatric symptoms such as affective (e.g. depression) and psychotic symptoms (e.g. hallucinations and delusions) is consistent with the profile of the IPA definition. That is, there were more individuals with any comorbid psychiatric symptoms among those with agitation (73% vs 82%) but this difference was not significant. This report illustrates how common this condition is even in MCI and its impact on function.

Evaluating the criteria using existing assessment tools

One of the challenges of using the IPA definition of agitation is the absence of tools that can provide

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reliable identification and symptom monitoring. In 2017, clinicians and researchers endeavored to address the need to develop an "IPA-informed" measure of agitation for clinical and research use. The goals were to develop an instrument that would reflect syndromic agitation consistent with IPA criteria and provide domain scores for the key features in criteria B of excessive motor activity, verbal aggression, and physical aggression. Ideally, the newly developed scale would incorporate information from multiple sources (i.e. patient, caregiver, and clinician), capture clinically meaningful effects, and demonstrate sensitivity to change in response to interventions. Scale performance would allow determination of effect sizes, allowing calculation of sample sizes and power studies. Subsequently, the Clinical Trials in AD – European and US (CTAD EU-US) Task Force on Agitation/Aggression endorsed the use of existing datasets to construct an evidence-based single novel measure of agitation by selecting item subsets of existing scales that best reflect the IPA criteria, and the situations in which agitation occurs (Sano *et al.*, 2018). A modified Delphi process was implemented to abstract IPA-specific items from the CMAI (Cohen-Mansfield, 1997) and the NPI-Clinician version (NPI-C) (De Medeiros *et al.*, 2010) for IPA agitation definition informed abstracted measures of agitation. All items from the CMAI were included, as were all items from the agitation, aggression, aberrant motor activity, abnormal vocalizations, disinhibition, and irritability/lability domains of the NPI-C. Through an iterative process described elsewhere (de Mauleon *et al.*, 2021), two sub-scales were described, which could be abstracted from the CMAI, (the 19-item CMAI-IPA) and the NPI-C (the 25-item NPI-C-IPA). Performance was then assessed in 262 participants in the French Agitation and Aggression AD Cohort (A3C) cohort (De Mauleon *et al.*, 2021), a 12-month longitudinal prospective observational cohort of memory clinic and long-term care patients designed to simulate a clinical trial. Abstracted measures were compared to each original scale for performance characteristics including minimally clinically important difference (MCID), sensitivity, specificity, area under the curve (AUC), sensitivity to change, test-retest reliability, accuracy, and predictive validity (de Mauleon *et al.*, 2021). Globally, all measures were reasonably similar, and all were internally valid. Measures had comparable AUCs and sensitivity to change and comparable ability to clinician ratings. However, abstracted measures were preferred as they were shorter, with some differences noted. For example, for meaningful clinical change, both the parent and abstracted CMAI measures had high endpoint scores, while the parent and abstracted NPI-C scores approached zero for those who were much improved. This may be due to the CMAI containing items not relevant to the IPA agitation definition (e.g. verbal non-aggression). Also, as a frequency measure without a severity component, the CMAI may not have fully captured change while both frequency and severity are captured in the clinician ratings in the NPI-C. With respect to domains of motor activity, verbal aggression, and physical aggression, internal consistency of the NPI-C-IPA was good, but for the CMAI Cronbach's alpha was low for verbal aggression and very low for physical aggression. Overall, the authors concluded that internal consistency and reliability analyses demonstrated better accuracy for NPI-C-IPA compared to CMAI-IPA, with NPI-C-IPA also being more clinically relevant (de Mauleon *et al.*, 2021). The domain analyses address a remaining controversy within the agitation definition concerning the clustering of these behaviors and this report reinforces the need for further research on this topic. These initial data suggest that the IPA agitation definition is relevant and robust, as measured by established scales and novel abstracted measures.

Reconsideration of the definition of agitation in cognitive disorders: removing provisional

Survey procedures and results

To accomplish reconsideration of the IPA agitation definition, the current ADWG followed the same process as that of the provisional definition. The goal of the process was to preserve the criteria wherever possible to allow continuity for past, ongoing, and planned studies while incorporating the advances suggesting that the criteria are no longer "provisional." A survey was sent to IPA members and members of affiliated organizations asking for perspective on the criteria as a whole as well as on each component. The survey was disseminated three times over a 6-week period from January 10, 2020 to Feb 5 2020 to 5233 emails. Of these 2169 were opened (41.4%), 3029 were unopened (57.9%) and 24 erroneously directed (0.5%). There were 192 respondents with 169 complete (88.0%) and 23 partial (12.0%) responses, representing individuals from 40 countries. A majority (62.43%) had been in the field of Psychogeriatrics for 16 or more years. Thirty-eight percent of respondents had used the criteria in their practice; 11% had participated in conducting a clinical trial that used the criteria; and 10% had used the criteria in non-trial research. Use of the criteria was greater for clinical care than for research among these respondents. Research application was equally divided between interventional and non-interventional research. Specific items and comments were reviewed at a consensus meeting with the ADWG. Results of the survey of the IPA

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Table 1. Results of survey sent to the IPA members and members of affiliate organizations

Question	N Responded	Yes (%)	No (%)	Not applicable (%)
Have you used the IPA agitation criteria in your practice?	172	37.79	51.74	10.47
Have you participated in a clinical trial that used IPA agitation criteria?	172	10.53	77.78	11.07
Have you participated in non-trial clinical research that used IPA agitation criteria?	172	9.88	77.91	12.21
Do you concur with removing "provisional" from the label of the IPA agitation criteria?	172	90.12	9.88	–
Do you agree with Criterion A defining multiple cognitive disorders in the IPA agitation definition?	15	80.00	20.00	–
Do you agree with Criterion B defining three key domains of agitation as stated in the IPA agitation criteria?	15	46.67	53.33	–
Do you agree with Criterion C of the IPA agitation criteria requiring that the behaviors are sufficient to impair interpersonal relationships, social functioning, or activities of daily living?	15	73.33	26.67	–
Do you agree with Criterion D of the IPA agitation criteria requiring that the behaviors are not attributable solely to another psychiatric disorder, medical condition, or the physiological effects of a substance?	14	57.14	42.86	–

and affiliated organization membership are summarized in Table 1. There was wide support of adjusting the title of the criteria by removing the word "provisional" (90.1% approved). Responses to the individual elements were low ($N = 15$) as many who accepted the criteria as a whole did not comment on individual elements.

We assembled the ADWG whose membership overlapped with but was not identical to the membership of the previous work group. A planning meeting with members of this group acknowledged the need to remove "provisional" from the title of the criteria. The group also notes that there were conditions, settings, and circumstances beyond those considered at the time of the creation of the current criteria that warranted modifications specific to those circumstances. To address these needs a consensus meeting took place on October 23, 2021 in which both final criteria and needs for adjustment to special settings were summarized. Survey results were summarized at the consensus meeting and the ADWG provided the final determination of any modification. Below we summarize the discussion around each of the four criteria.

For Criteria A, 80% of respondents concurred with the language as written. A few survey respondents ($N = 4$) commented on the need to consider whether to include Diagnostic and Statistical manual (DSM) and International Classification of Disease (ICD) coding terminology around mild and major "neurocognitive" conditions. However, the consensus was that "cognitive impairment" was the least restrictive and avoided integrating terms that may be subject to frequent updates. Thus, no adjustment was made to this criterion.

While strongly endorsed, there were several survey comments to Criterion B. A small number of survey respondent were concerned about distinguishing agitation behaviors from delirium or distress due to environmental factors including inadequate care. The working group acknowledged that environmental situations should be addressed. However, if the best attempts to correct the environment do not mitigate the distress or the behaviors, the working group determined that persistence of both behavior and perceived distress would meet the criteria for agitation.

Another concern was in the grouping of the verbal and physical aggression with agitation. Here the working group focused on the overall experience of clinicians as well as on the available data on agitation. Most studies do not separate these behaviors. The working group acknowledged that this may be the result of the current tools but that grouping of these behaviors reflect the perspective of both clinicians and families in defining this condition, leading the working group to maintain the current descriptions. Several commented about the criterion of 2 weeks duration, especially in the special circumstances described below which may not permit waiting that long. To address this, supplemental comments were added to the criteria to acknowledge these circumstances.

Several comments from the survey on Criterion C ($N = 5$) remarked that it could be difficult to demonstrate excess disability in an individual with advanced dementia. One proposal included

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Table 2. International Psychogeriatric Association consensus clinical and research definition of agitation in cognitive disorders

Criterion A. The patient meets criteria for a cognitive impairment or dementia syndrome (e.g. AD, FTD, DLB, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder).
Criterion B. The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g. rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of two weeks or the behavior represents a dramatic change from the patient's usual behavior*.
(a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms).
(b) Verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting).
(c) Physical aggression (e.g. grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property).
Criterion C. Behaviors are severe are associated with excess distress or produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:
(a) Significant impairment in interpersonal relationships.
(b) Significant impairment in other aspects of social functioning.
(c) Significant impairment in ability to perform or participate in daily living activities.
Criterion D. While comorbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, medical condition, including delirium, suboptimal care conditions, or the physiological effects of a substance
* In special circumstances the ability to document the behaviors over two weeks may not be possible and other terms of persistence and severity may be needed to capture the syndrome beyond a single episode

describing excess distress or disability and the working group accepted this minor modification.

For Criterion D the responses reiterated the need to address delirium and thus the word "delirium" was added as an example of a medical problem.

Throughout the course of the IPA criteria review, only these minor adjustments beyond the proposed change in title were found to be necessary. The final criteria are shown in Table 2. Survey respondents as well as other feedback to the ADWG encouraged development of "case studies" that would provide examples of how to apply the criteria in specific situations, and the working group endorsed this activity.

Special circumstances in which agitation can be observed

In the course of reviewing the criteria for agitation in cognitive disorders, a number of special circumstances not anticipated in the original process of definition development were identified. In some cases, these require adjustments in the criteria to facilitate their real-world application.

Terminal agitation

Terminal agitation occurs in the final months of life in persons with fatal illnesses and is common in dementia, occurring in approximately half of the individuals (Sampson *et al.*, 2019, 2018). Delirium is common in this setting as organ failure advances in the terminal period. The IPA criteria can be used in this situation, but the exclusion criteria (e.g. medical illness) may require adjustment to reflect the failing physical health of these individuals.

Acute agitation

Agitation may have an acute onset, beginning abruptly in provocative environmental or physiological circumstances including vesperal agitation (e.g. sundowning), hospitalization, movement to an unfamiliar environment (e.g. nursing home), drug-related agitation, drug or alcohol withdrawal, delirium, and pain (Carrarini *et al.*, 2021). The IPA criteria require that agitation be present at least intermittently for the past two-week period and would not apply to acute agitation. Behaviors of the agitation episode identified by the IPA criteria apply to acute agitation, and the criteria can be applied after adjusting for the duration. Management of acute agitation differs from that of managing chronic agitation; the need to evaluate the individuals for delirium stemming from medical illness (e.g. pneumonia, urinary tract infection) is more urgent. Pharmacologic management may be needed during acute episodes to facilitate necessary evaluations (Meehan *et al.*, 2002).

Agitation occurs in up to 15% of older people hospitalized for medical illnesses (Mansutti *et al.*, 2020) and is more common (up to 30%) in those admitted to intensive care units (Almeida *et al.*, 2016). Delirium is common among agitated hospitalized patients; dementia is a risk factor for delirium, and delirium is a risk factor for subsequent development of dementia (Fong *et al.*, 2015). People

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with agitation in the hospital setting would be identified by IPA criteria although adjustments for duration of agitation and the role of medical illnesses in causing agitation would require adjustment.

Agitation in the ED

Agitation is common in older adults treated in the ED and can be particularly acute in severity and challenging to manage in this setting. The most common diagnostic question is whether agitation can be attributed to dementia itself or to superimposed delirium (Fong *et al.*, 2015). Delirium can be defined as a mental status change of acute onset associated with inattention and disturbed cognition, often fluctuating, and due to medications or medical conditions. The IPA agitation criterion specifying that agitation be of at least two weeks' duration should make this a distinction straightforward since the time course of delirium is generally much shorter, but in practice this depends on being able to take an accurate history from a reliable informant. The ED clinician may not have ready access to such an informant particularly for patients who reside in long-term care. The differential diagnosis is important because approaches to managing agitation may be very different in dementia (nonpharmacologic, including psychosocial and environmental interventions first, medications second) and delirium (find the medical cause and treat) (Kales *et al.*, 2014). To this end, ED clinicians are making increasing use of structured delirium assessments such as the Brief Confusion Assessment Method (bCAM) (Han *et al.*, 2013), the Delirium Triage Screen (Han *et al.*, 2013), and the Richmond Agitation Sedation Scale (Han *et al.*, 2015), as well as structured delirium interventions such as the ADEPT tool (Shenvi *et al.*, 2020). As in the case of acute agitation, patients with agitation in the ED would be identified by IPA criteria although adjustments for duration of agitation and the role of medical illnesses in causing agitation would require adjustment.

Agitation in specific conditions of cognitive impairment

Traumatic brain injury (TBI) is a cause of cognitive impairment and concomitant agitation. Other conditions with cognitive impairment including Huntington's disease and human immunovirus (HIV) dementia may also produce agitation. Forms of agitation that occur in this population include intermittent explosive disorder and the behavioral dyscontrol/impulsive aggression observed in the traumatic encephalopathy syndrome related to chronic traumatic encephalopathy (CTE) (Mosti & Coccaro Summer 2018, Katz *et al.*, 2021). Some individuals with these syndromes will meet the IPA criteria for agitation. A history of TBI or of repetitive mild head injury will assist in identifying this special circumstance.

Disinhibition may co-occur with agitation and a hyperactivity-impulsivity-irritability-disinhibition-aggression-agitation cluster has been identified in AD and other dementias (Keszycki *et al.*, 2019). This cluster may correspond to the "excessive motor activity" criterion of the IPA agitation definition. As noted, the relationship of agitation to aggression is ambiguous. Some of the major behaviors identified in the IPA agitation criteria include aggression (e.g. verbal aggression, physical aggression); the criteria also include non-aggressive behaviors (e.g. excessive motor activity). Reactive and proactive types of aggression have been identified (Wrangham, 2018). The two types of aggression have differing cognitive correlations, genetics, animal models, and treatments (Waltes *et al.*, 2016, Bertsch *et al.*, 2020). Patients with cognitive impairment and aggression tend to have the reactive form with agitation occurring with unmet and unidentified needs, lack of understanding as cognition declines, and specific biological changes that lower the threshold for aggression or promote agitation and aggression (Senanarong *et al.*, 2004, Volicer, 2021). Patients with reactive aggression would be identified by the IPA agitation criteria. Premeditated proactive aggression is less common in cognitive impairment syndromes, although it may occur in the setting of dementia-related psychosis and delusional beliefs (Volicer, 2021).

Implementation of the IPA consensus clinical and research definition of agitation in cognitive disorders

Progress has been made in identifying and defining agitation in cognitive disorders. More needs to be done to disseminate these criteria, educate families and practitioners about agitation in cognitive disorders using these criteria, and advance new research on agitation in cognitive disorders. A key unmet need is to understand the relationship between caregiver and clinician perspectives on agitation. Data suggest that families tend to use a different vocabulary to describe agitation and to attribute it to causes that differ from those identified by the clinician (Polenick *et al.*, 2018, Gilmore-Bykovskyi *et al.*, 2020). Educating clinicians and family caregivers will improve care for patients with agitation and cognitive impairment. Initiatives to advance achievement of this goal include operationalizing the IPA agitation criteria and using the criteria terminology, that is excessive motor activity, verbal aggression, physical aggression, creating checklists to facilitate

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identification of agitation, and using case studies to illustrate best practices in agitation management. In an effort to assist clinicians in implementing the IPA definition in identification and management of dementia, the ADWG constructed an algorithm guiding the use of psychosocial and pharmacologic interventions to ameliorate and prevent agitation (Cummings, in review). The wide array of circumstances in which agitation occurs, home, nursing homes, hospital wards, intensive care units, EDs, indicate that educational efforts reaching many patient care venues are warranted. Education on agitation must be time- and context-specific to meet information needs of busy clinicians.

Additional studies of the IPA agitation criteria are needed. Efforts toward prospective validation of the criteria against clinician's diagnosis of agitation and rating scales used to characterize agitation would strengthen the criteria. Inter-rater reliability studies would provide insight into which aspects of the criteria are least clear or most difficult to apply. International studies would provide information on how well the criteria perform across a variety of cultural and linguistic settings. Criterion C of the IPA definition pertaining to the key symptoms of the agitation syndrome had the least support and the most suggestions in the survey the working group conducted. Further exploration of how to define the symptoms is warranted. This review suggests that the IPA criteria can be applied to diverse circumstances with adjustments for duration or causation by medical illness or physiological effects of a drug. Processes to standardize such adjustments are needed.

Conclusions

Agitation is common in individuals with cognitive impairment and defining agitation has a key role in facilitating descriptive, interventional, non-interventional, and biological research. The IPA provisional consensus clinical and research definition has functioned well and has been widely used in interventional and non-interventional research. The criteria have advanced sufficiently that the label of "provisional" is no longer appropriate. The deliberations of the ADWG and survey results support removal of "provisional" from the title. Other changes to the definition or to individual criteria are not proposed; continuity with the current definition is important for recently completed, ongoing, and planned research. It is the goal of the IPA to promote excellent care and research of older adults with behavioral and mental health needs. The IPA agitation definition is one aspect of achieving this goal.

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Conflict of interest

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All authors are members of the IPA Agitation Work Group. All authors participated in conceptualizing, reviewing, and editing the manuscript. All authors approved the final version of the manuscript.

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