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Research Article

Safety of Disclosing Amyloid Imaging Results to MCI and AD Patients

Carl Taswell

Brain Health Alliance, Ladera Ranch, CA, USA and Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

Cheryl Donohue

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

Maree T. Mastwyk

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

Andrea G. Louey

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

Jacqueline Giummarra

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

Joanne Robertson

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

David G. Darby

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

Colin L. Masters

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia

Christopher C. Rowe

Florey Inst Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia and Austin Health Dept Molecular Imaging, Melbourne, VIC, Australia

ABSTRACT

Objective: To assess the psychological impact of disclosing a positive or negative amyloid brain scan result to symptomatic individuals with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD).

Design: Prospective longitudinal cohort study.

Setting: Florey Institute of Neuroscience & Mental Health, University of Melbourne, Australia.

Participants: A total of 133 individuals aged 50–85 with MCI or mild AD enrolled in the study with data collected between October 2014 and June 2016.

Interventions: Disclosure of amyloid imaging results to participants.

Measurements: Positron emission tomography (PET) brain amyloid imaging with [18F]-NAV4694; psychometric scales including the Center for Epidemiologic Studies Depression (CES-D) scale, Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scales (HADS-A and HADS-D) and State-Trait Anxiety Inventory (STAI) performed before and after disclosure of amyloid imaging results.

Results: We did not observe any worsening of psychological health with a panel of psychometric scales assessed on individuals to whom amyloid brain scan results were disclosed.

Conclusions: We consider it safe, without apparent risk of harm to patients, to disclose amyloid imaging results to patients who have no prior history of neuropsychiatric illness.

Keywords: Alzheimer's disease, Dementia, Mild cognitive impairment, PET scan, Brain amyloid imaging, Risk disclosure

Introduction

As the most common of the dementias, Alzheimer's disease (AD) imposes an overwhelming challenge for the affected individuals, a difficult emotional burden for their families and caregivers, and a substantial financial burden for the communities and public health agencies that must cope with the cost of dementia care [1,2]. Optimism for discovering interventions to delay onset, slow progression and find a preventive cure for AD remains focused on research advances with the development and validation of biomarkers defined as measurable indicators of biological state in the human body [3]. AD biomarkers include those observable directly by ex vivo laboratory testing of blood, fluid and tissue samples as well as indirectly by in vivo medical imaging of brain features, both structural and functional. PET brain imaging for biomarkers of dementia, targeting beta-amyloid in extracellular plaques and tau in intraneuronal tangles, now allows more definitive diagnosis relevant to an individual's future health [4].

Development of PET radiotracers for amyloid imaging has preceded, and progressed more rapidly, than that for tau imaging [5,6]. Consequently, these radiotracers for PET brain scans have currently been approved by the FDA only for amyloid imaging but not yet for tau imaging [7]. A systematic review and meta-analysis of 19 studies investigating 682 patients with AD demonstrated that amyloid imaging differentiates AD patients from normal controls with a sensitivity of 89-90% and specificity of 87-88% [8]. However, another meta-analysis of amyloid imaging demonstrated that the prevalence of cerebral amyloid pathology increased from 10% at age 50 to 44% at age 90 in persons with normal cognition [9]. Therefore, interpreting results from amyloid imaging for a specific individual requires judicious consideration and review of all clinical data available for that individual patient [7].

Moreover, balancing the right to access this personal health information, when assessed in either clinical or research studies, raises important ethical questions about benefits and risks for the patient. As a field, medical genetics with genetic counseling has developed experience with susceptibility testing and risk disclosure for AD with the apolipoprotein E genotype as a biomarker [10-14]. However, this genetic counseling experience has not involved amyloid imaging as a biomarker for AD. Other recent publications devoted to the medical ethics of susceptibility testing and risk disclosure discuss more directly the issues related to amyloid imaging as a prognostic biomarker for AD [15-18].

These issues consider both the validity of the biomarker and the impact on the patient when evaluating the potential benefits and harms of disclosing amyloid imaging results to a patient. A concerned person with a negative scan may benefit from reassurance, but a vulnerable person with a positive scan may risk anxiety and depression when informed about the current dearth of proven effective treatments for AD. A previous study on the safety and tolerability of disclosing amyloid imaging results to patients has been completed [19]. However, this study was limited to a small sample size of subjects (N=11) imaged with positive amyloid scans (N=4).

Therefore, the present study reported in this article was performed with a much larger sample size of subjects (N=133) imaged with positive amyloid scans (N=104) to assess the psychosocial impact of disclosing a positive or negative amyloid brain scan result to symptomatic individuals with either mild cognitive impairment (MCI) or mild AD. Formally, this study investigated the statistical null hypothesis of no change in psychological status of subjects before and after scan results disclosure as measured by various mood scales for the assessment of anxiety and depression.

Methods

The clinical trial was registered at www.anzctr.org.au and www.trialadviser.com with all participants signing informed consent prior to entering the study. Participants were enrolled in the study with data collected between October 2014 and June 2016. Because the protocol for the clinical trial was approved by the local IRB and the investigation began prior to publication of the recommendations by Harkins et al. [18] for cognitively normal adults, an approach comparable (ie, similar but not identical) to that recommended by those guidelines were incorporated in this trial for MCI and AD patients. The patient population included individuals with subjective and/or objective symptoms involving complaints about memory and cognition. Patients were recruited from referrals by specialist physicians (geriatricians, neurologists, psychiatrists) working at memory disorder public clinics or private practice offices in Victoria, Australia.

Inclusion criteria were specified as age 50-85, probable amnestic mild cognitive impairment or mild Alzheimer's dementia with a Clinical Dementia Rating (CDR) score of 0.5 or 1.0, English speaking with at least 6 years education, able to complete psychological testing and brain imaging, and presence of a companion who could serve as a responsible person and study partner for the patient. Exclusion criteria were specified as any unstable medical condition within the past 5 years, a history of cancer (except for nonmelanoma skin cancer and in situ prostate cancer), or any neurological illness (such as epilepsy, stroke, Parkinson's disease) unrelated to the inclusion criteria of MCI or AD. This cohort with total size N=133 also excluded individuals with any other current or prior psychiatric condition (including psychotic, mood and substance use disorders) that could interfere with psychological testing. All patients referred into the study had cognitive symptoms reported by the individual and/or by the informant. Information about patient symptoms was obtained from referring physician letters and from separate structured clinical interviews performed at the University of Melbourne by a nurse practitioner, psychologists and a neurologist. Patients were interviewed, and a battery of

memory and cognition tests completed to confirm eligibility. These tests included the CDR, the CDR Scale Sum of Boxes (SOB), the Mini Mental State Examination (MMSE), and the Functional Assessment Questionnaire (FAQ). Patients were then classified into diagnostic categories based on standard criteria for cognitive impairments, using the NIA-AA revised criteria for MCI [20] and AD [21], as determined by clinical evaluation supported by these functional ability and cognition tests prior to any amyloid imaging.

PET brain scans were scheduled and the patients together with their study partners were provided counseling by a University of Melbourne investigator (a behavioral neurologist) about the reasons for and possible results of these scans but were not given any definitive diagnosis prior to the scans. For example, they were educated about an estimated percentage risk of 65–70% for incurring Alzheimer's disease pathology implied by a positive amyloid scan when associated with a clinical presentation of amnestic MCI. This risk estimate was based on past local experience at University of Melbourne. This study was not designed to be a randomized, placebo controlled and blinded study with different pharmaceutical treatments or intervention arms of the investigation.

All participants signed consent expecting to be informed of the results of the amyloid brain scans and to be shown images of their own amyloid brain scans. The consent form used in the study, formally the Participant Information and Consent Form (PICF), complied with standards established by the Australian National PICF Program, explained the process of disclosure and served as the formal document used as part of the education and counseling provided to all participants prior to amyloid imaging. Therefore, this study was also not designed to be randomized with respect to being scanned or being informed of the results because all participants acknowledged the goals of providing the scan results to their referring physicians in order to support their clinical evaluations, and to source patients possibly eligible for clinical trials with pharmaceutical treatments or other interventions. Thus, all subjects were treated in the same consistent manner for the present study reported here on the psychological impact of disclosing amyloid imaging results to patients. All participants in the identified cohort opted in to the study for both amyloid imaging and results disclosure, all completed brain amyloid scans, and none subsequently changed their minds, raised objections to learning results or otherwise opted out of the study.

For the PET brain scans, [18F]-NAV4694 (Navidea Biopharmaceuticals) amyloid imaging was performed as described previously [22]. This amyloid imaging agent has not yet been approved in Australia for routine clinical use, and currently remains limited to use in clinical research trials. The disclosure to patients of PET scan results was done for clinical purposes initially by the referring physician (to whom the results were provided after being read as a binary result of positive or negative for amyloid without any quantitative value) prior to the subsequent visit for research purposes in this study with psychometrics for mood scales. Both the initial disclosure by the referring physician and the subsequent disclosure by University of Melbourne investigators were always completed within a time interval of one week for both disclosures for each participant. All disclosures were done with presentation of the scans as pictures and discussion of the meaning of the results answering any questions. The discussion about the scans was then followed by a discussion about available trials if appropriate for the participant. Before-scan counseling and after-scan disclosures were completed within approximately three months and were done with both the patients and their study partners. Disclosures were not done with patients alone due to the risk of them not recalling the information. Assessment of comprehension of the information provided to both patients and their study partners were not done at the time of the before-scan counseling or after-scan disclosures but was later evaluated by self-administered questionnaires at the time of a subsequent review at six months.

For this psychological impact study, participants were evaluated with a panel of psychometric scales for evaluation of mood both before and after disclosure of scan results with median intervals of 91 days between the before and after assessments, 35 days between the before assessment and the amyloid scan, and 57 days between the amyloid scan and the after assessment. These mood scales included the Center for Epidemiologic Studies Depression (CES-D) scale [23], the short form version of the Geriatric Depression Scale (GDS) [24], the Hospital Anxiety and Depression Scales (HADS-A and HADS-D) [25] and the short form version of the State-Trait Anxiety Inventory (STAI) [26]. Cohen's d effect size, Gosset's t test (aka Student's t test) and Wilcoxon's t test (aka sign-rank test) were analyzed for the statistical null hypothesis of no change in psychological status on each of the mood scales for various subgroups of the study cohort selected demographically by age, clinical diagnosis and imaging result. As mentioned above, clinical diagnoses were made prior to the imaging scan and thus without knowledge of the amyloid imaging result.

All statistical analyses were performed with paired samples for the repeated measures of before and after on each subject. This use of paired analyses means that all change scores were calculated on an individual-wise base, and not on a pooled or group-wise basis. Thus, change scores for each psychometric scale were calculated for everyone by subtracting the individuals before score from the after score, resulting in the positive or negative change scores and positive or negative effect sizes that appear in the results tables. All results tables display the 25%, 50% and 75% percentile values of the score distributions for each mood scale as the before, after and paired change values.

Results

For participants who completed amyloid scans (N=133), there were 99 with MCI and 34 with AD assumed as clinical

diagnoses for the purpose of subgroup analysis in this study. Figure 1 displays amyloid positive and negative examples of PET brain scans in the sagittal and axial planes. Table 1 summarizes the patient demographics for the entire study cohort and the subgroups selected by age, clinical diagnosis, and amyloid imaging. Table 2 lists Cohen's d effect size, Gosset's t-test P value and Wilcoxon's t-test P value for the before-after paired analyses of subjects from the entire cohort for which the null hypothesis was not rejected if either P value exceeded the 0.005 threshold [27].

The corresponding analysis with hypothesis test results are presented respectively in Table 3 for the age subgroups, Table 4 for the clinical diagnosis subgroups and Table 5 for the amyloid imaging subgroups. In these tables, the medians (50th percentile values) of the actual psychometric scale scores are displayed in the columns 'Before', 'After' and 'Change' for the individual paired differences. As a measure of dispersion around the central tendency of the score distributions, the corresponding values for the interquartile range from the 25th to 75th percentiles are also listed. For example, in Table 2 for the mood scale GDS, the individually paired change scores (the difference between before and after for each subject) were -1 at the 25th percentile, 0 at the 50th percentile and +1 at the 75th percentile.

For participants sub-grouped by age or clinical diagnosis who completed psychometrics on mood scales before and after disclosures, the null hypothesis could not be rejected for any of the scales. For participants with positive amyloid scans who completed psychometrics before and after (N=82-85, see each mood scale for the positive subgroup in Table 5), the null hypothesis could not be rejected for any of the scales. As published in our preliminary report [28], for participants with negative amyloid scans who completed psychometrics (N=22-24, see each mood scale for the negative subgroup in Table 5), the null hypothesis could only be rejected possibly for GDS or STAI when adhering to the conventional threshold value of $P \leq 0.05$. However, any statistical hypothesis test that results in a P value declared 'significant' by convention of a value ≤ 0.05 must still be evaluated for the occurrence of both Type I errors (false rejection of a true null hypothesis) and Type II errors (false acceptance of a false null hypothesis).

Therefore, any statistical result must always be interpreted with a common-sense re-examination of the data that includes either clinical and/or scientific tests of practical validation (for which such a validation criterion should be independent of statistics and probability). As a consequence, in the preliminary report [28], we considered the rejection of the null hypotheses for GDS on the amyloid negative subgroup a misleading statistical artifact resulting from a Type I error because the actual median score for the subgroup changed only from 2 to 3 where the median paired score change was only +1, well within the normal range for the GDS scale. A similar argument applies to STAI on the amyloid negative subgroup because the median score changed only from 9 to 10 where the median paired score change was only +1, also within the normal range for the STAI scale. Further, the amyloid negative subgroup had the smallest sample size (N=29) of the subgroups, significance from the Wilcoxon's paired t tests exceeded P>0.05, and none of the effect sizes reached a threshold of d>0.5, suggesting that noise with a Type I error remains a reasonable explanation for what we inferred to be statistical artifacts.

Thus, there was no practical clinical change in the before and after psychometrics about anxiety and depression on any of the mood scales for subjects with disclosure of either positive or negative amyloid scans within a time interval of approximately 3 months between the before-scan counseling and the afterscan disclosures. Moreover, the rate of Type I errors for falsely rejecting the null hypothesis can be reduced by decreasing the P value threshold. Indeed, with the strong support just

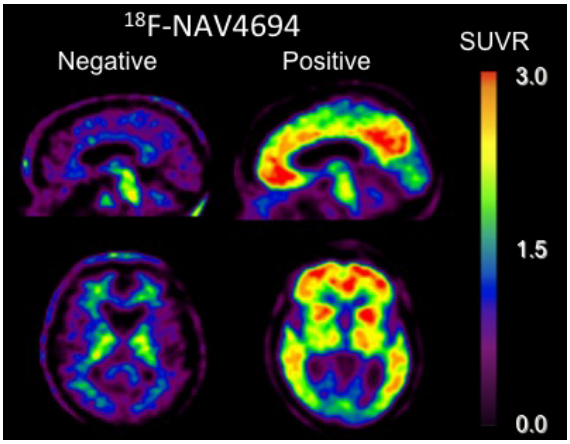

Figure 1. Amyloid negative and positive examples of PET brain scans with F18-NAV4694

Table 1. Patient demographics for subgroups in study cohort

Subgroup description	Subgroup size N			Age at PET scan		Cognitive scale medians			
	Total	Male	Female	Median	Min-Max	MMSE	FAQ	CDR	SOB
Entire Cohort	133	72	61	70.9	51.5-85.5	24	7	0.5	2.5
Age Younger <70	58	29	29	64.5	51.5-69.8	24	7	0.5	2.5
Age Older ≥ 70	75	43	32	76.2	70.5-85.5	25	7	0.5	2.5
Diagnosis MCI	99	54	45	72.3	51.5-85.2	25	6	0.5	2.5
Diagnosis AD	34	18	16	70.5	52.3-85.5	23	11	1	4
Amyloid negative	29	1	10	69.1	51.6-85.2	25	7	0.5	2.5
Amyloid positive	104	53	51	72.2	51.6-85.5	24	7	0.5	2.5

Table 2. Results from entire cohort

Scale	Effect size and significance for paired t tests				Mood scale percentiles (25%, 50%, 75%)		
	Cohen's d	Gosset's P	Wilcoxon's P	Size N	Before	After	Paired change
CES-D	+0.041	0.673	0.693	105	(3, 6, 8)	(3, 5, 11)	(-4, 0, +3)
GDS	+0.192	0.047	0.099	109	(0, 2, 3)	(1, 2, 4)	(-1, 0, +1)
HADS-A	+0.022	0.821	0.863	107	(2, 4, 6)	(1, 4, 6)	(-2, 0, +2)
HADS-D	-0.015	0.879	0.909	107	(1, 2, 5)	(1, 2, 4)	(-1, 0, +1)
STAI	+0.156	0.106	0.253	106	(7, 9, 12)	(7, 10, 13)	(-1, 0, +2)

Table 3. Results from age subgroups: younger < 70 and older ≥ 70

Subgroup	Scale	Effect size and significance for paired t tests				Mood scale percentiles (25%, 50%, 75%)		
		Cohen's d	Gosset's P	Wilcoxon's P	Size N	Before	After	Paired change
Younger	CES-D	+0.046	0.766	0.537	42	(4, 7, 12)	(2, 6, 12)	(-6, 0, +2)
	GDS	+0.283	0.068	0.094	44	(1, 2, 3)	(1, 3, 5)	(-1, 0, +2)
	HADS-A	+0.048	0.752	0.981	44	(3, 5, 7)	(2, 4, 8)	(-2, 0, +2)
	HADS-D	-0.182	0.233	0.230	44	(1, 2, 5)	(1, 2, 4)	(-2, 0, +2)
	STAI	+0.213	0.174	0.320	42	(8, 10, 12)	(7, 11, 14)	(-1, 0, +3)
Older	CES-D	+0.037	0.768	0.920	63	(2, 5, 10)	(3, 4, 10)	(-4, 0, +3)
	GDS	+0.119	0.342	0.513	65	(0, 1, 3)	(1, 1, 3)	(-1, 0, +1)
	HADS-A	+0.000	1.000	0.817	63	(1, 4, 5)	(1, 3, 5)	(-2, 0, +2)
	HADS-D	+0.152	0.233	0.249	63	(0, 1, 4)	(1, 1, 3)	(-1, 0, +1)
	STAI	+0.118	0.347	0.516	64	(7, 9, 12)	(7, 10, 12)	(-1, 0, +1)

Table 4. Results from clinical diagnostic subgroups: MCI and AD

Subgroup	Scale	Effect size and significance for paired t tests				Mood scale percentiles (25%, 50%, 75%)		
		Cohen's d	Gosset's P	Wilcoxon's P	Size N	Before	After	Paired change
MCI	CES-D	-0.037	0.740	0.329	79	(3, 6, 12)	(2, 5, 11)	(-5, -1, +2)
	GDS	+0.192	0.085	0.170	82	(0, 2, 3)	(1, 2, 4)	(-1, 0, +1)
	HADS-A	+0.047	0.674	0.796	80	(2, 4, 6)	(1, 4, 6)	(-2, 0, +2)
	HADS-D	-0.035	0.755	0.673	80	(1, 2, 4)	(1, 2, 4)	(-1, 0, +1)
	STAI	+0.114	0.316	0.501	79	(7, 10, 12)	(7, 10, 14)	(-2, 0, +2)
AD	CES-D	+0.264	0.190	0.316	26	(0, 6, 11	(3, 5, 12)	(-3, +1, +4)
	GDS	+0.191	0.331	0.358	27	(1, 2, 3)	(0, 2, 4)	(-1, 0, +2)
	HADS-A	-0.055	0.779	0.319	27	(2, 4, 6)	(1, 3, 5)	(-2, 0, +1)
	HADS-D	+0.042	0.828	0.542	27	(0, 2, 6)	(1, 2, 4)	(-1, +1, +1)
	STAI	+0.305	0.125	0.114	27	(7, 9, 12)	(8, 10, 13)	(0, +1, +1)

Table 5. Results from amyloid imaging subgroups: negative and positive

Subgroup	Scale	Effect size and significance for paired t tests				Mood scale percentiles (25%, 50%, 75%)		
		Cohen's d	Gosset's P	Wilcoxon's P	Size N	Before	After	Paired change
negative	CES-D	+0.135	0.535	0.896	22	(3, 6, 10)	(2, 4, 14)	(-3, 0, +2)
	GDS	+0.422	0.050	0.071	24	(1, 2, 3)	(1, 3, 5)	(0, +1, +2)
	HADS-A	+0.346	0.104	0.083	24	(2, 3, 5)	(1, 4, 7)	(-1, +1, +2)
	HADS-D	-0.045	0.826	0.676	24	(1, 2, 3)	(1, 2, 3)	(-2, 0, +1)
	STAI	+0.445	0.040	0.072	24	(7, 9, 12)	(8, 10, 13)	(-1, +1, +3)
positive	CES-D	+0.005	0.962	0.588	83	(2, 6, 12)	(3, 5, 11)	(-5, 0, +3)
	GDS	+0.124	0.258	0.353	85	(0, 2, 3)	(1, 2, 4)	(-1, 0, +1)
	HADS-A	-0.085	0.440	0.300	83	(2, 4, 6)	(1, 4, 6)	(-2, 0, +2)
	HADS-D	-0.005	0.965	0.917	83	(1, 2, 5)	(1, 2, 4)	(-1, 0, +1)
	STAI	0.071	0.522	0.777	82	(7, 10, 13)	(7, 10, 13)	(-1, 0, +1)

recently published [27] for lowering the convention for P value thresholds from 0.05 to 0.005, we can now report accept instead of reject for the GDS scale, and as previously published, continue to report accept instead of reject for all other mood scales in Tables 2-5. Thus, we maintain our previously reported statistical inference that the null hypothesis of no change could not be rejected for any of the mood scales [28].

Because these analyses with subgroups by demographic categories as independent variables and mood scales as dependent variables, summarized above and reported in Tables 3-5 in which the study data was partitioned group-wise into different categories, failed to identify any risk of harm in any subgroup, we did not expect that a more finely partitioned point-wise analysis of the data would reveal any findings of either statistical or practical significance. Nevertheless, we also performed linear regression analyses to examine for the possibility of any association between any of the mood scale results as the dependent variables, and the subject age, subject MMSE score, and the number of days for the time intervals between pre-scan and scan, scan and post-scan, and pre-scan and post-scan visit dates as the independent variables. All linear regression R^2 values were essentially negligible or zero: for subject age, from a low of 0.001 on HADS-A to a high of 0.055 on HADS-D; for subject MMSE score, from a low of 0.000 on CES-D to a high of 0.023 on HADS-A; and for the time intervals between pre-scan, scan and post-scan visit dates, from a low of 0.000 on STAI to a high of 0.036 on GDS. Therefore, these linear regression analyses also failed to demonstrate any association between any of the independent and dependent variables.

Discussion

Our study presented here addresses the question of a possible change in psychological status of subjects, as measured by mood scales for symptoms of anxiety and depression, in response to disclosure of amyloid imaging results. The findings of our study should be considered in the context of what's known in the published literature about mood symptoms and brain imaging in relation to neurodegenerative and neuropsychiatric disorders which we review briefly here. A longitudinal pattern of worsening depressive symptoms may be associated with dementia as a prodromal feature but has not been proven to increase the risk for dementia [29,30]. Apathy has been associated with hypometabolism in the parietal regions, as measured by F18-FDG PET brain metabolic imaging, for patients in early stages of AD [31]. For non-AD patients identified as suffering depression or borderline personality disorder, suicidality has been associated with hypometabolism in the orbito- and pre-frontal regions [32]. For cognitively normal older adults, psychiatric symptoms including mood changes, anxiety and loneliness have all been associated with cortical amyloid burden [33-36]. Collectively, these studies support considerations of the use of brain imaging biomarkers when monitoring selected populations screened for the presence of psychiatric symptoms as indicators of a potential prodromal stage of AD.

Based on our findings of no harm observed as reported in the present study, we believe that the benefits outweigh the risks for disclosing to patients the results of PET brain amyloid imaging. Our results on a large sample size of N=133 patients with MCI or AD are consistent with the preliminary study of N=11 patients reported by Lim et al. [19] and the small study of N=42 patients reported by Wake et al. [37], as well as the larger study of N=97 cognitively normal older adults reported by Burns et al. [38]. Our study on N=133 cognitively abnormal patients advance beyond the study by Burns et al. [38] because their study was limited in the sense that it was done only on normal subjects and not on patients with MCI or AD. Our study of MCI and AD patients who had MMSE scores with mean 24 (± 2:7 SD) should also be contrasted with the study by Wake et al. [37] of asymptomatic patients who had MMSE scores with mean 29 (± 1:1 SD). Thus, from a practical clinical and societal perspective, our study will empower family medicine physicians, gerontologists, neurologists and psychiatrists with more relevant and credible information about MCI and AD patients that will better serve the needs and interests of other MCI and AD patients and their families. In simplest terms, we believe that MCI and AD patients want to know about the experience of other MCI and AD patients, not about the experience of normal healthy subjects.

Any clinical approach to screening and counseling for AD or research approach to selecting patients for AD studies with therapeutic agents, whether via psychiatric symptoms or via imaging biomarkers, should adhere to the ethical guidelines for appropriate use of PET brain amyloid imaging [39-43]. For research subjects and clinical patients who are scanned with amyloid imaging, ethical guidelines now also exist for how, when and what to tell them about the results [7,44-46]. The benefits of brain amyloid PET scans to clarify etiology and improve confidence about the most probable cause of cognitive impairment with subsequent disclosure of the amyloid imaging results to patients have been summarized with the following statement: "the 'value of knowing' allows for more effective medication management, engagement with support services, broaching of issues pertaining to driving and safety, and enrolment in clinical trials, among others" [41]. These advantages of disclosing results must always be weighed against the disadvantages for some patients who must consider possible adverse implications and consequences for continued employment or insurance with health coverage. Discussion of available clinical trials for the treatment of AD with the disclosure of imaging results in our study may have introduced a possible positive bias countering some of these potential disadvantages, and thus, remains a limitation of our study.

Furthermore, our study did not involve use of a measure of decisional regret such as the 5-item Decision Regret Scale intended for use at a given point in time [47]. However, we did not find any association in time on any of our mood

scales with R^2 values essentially zero for all linear regression analyses. Moreover, we are concerned with practical clinical psychosocial impacts on patients and their families rather than the theoretical limitations suggested by the omission of a decision regret scale in comparison with the overwhelming concordance of the consistent results from the reported use of multiple well-validated mood scales for anxiety and depression (see Tables 2-5). Of most practical significance throughout our clinical trial, there were no concerns expressed by any patients, family or caregivers about any real potential risk of harm to patients such as reports of suicidal ideation threats or plans, with or without visits to doctors' offices, psychiatric emergency rooms or hospitals for any such complaints.

Therefore, we consider it improbable that any potential use of a decisional regret scale would invalidate our results or conclusions. Instead, we believe that a more productive area of possible future research would be evaluation of mood scale psychometrics for the patient's primary caregiver instead of psychometrics for the patient. With continuing research on the validity of various imaging and non-imaging biomarkers and their association with different stages of AD, guidelines on the use of amyloid imaging and other biomarkers will continue to evolve [48,49].

Conclusions

Consistent with the foundational principle in medicine of first do no harm,[1] we examined whether disclosure of amyloid imaging results to patients might cause any harm by contributing to the development of anxiety and depression in these patients. We did not observe any worsening of psychological health with a panel of psychometric scales assessed on individuals to whom amyloid brain scan results were disclosed. We consider it safe, without apparent risk of harm to patients' mental health, to disclose amyloid imaging results to patients who have no prior history of neuropsychiatric illness.

Description of author's roles

C. Taswell performed the statistical data analysis, completed the literature review and wrote the article. C. Donohue, A. Louey, J. Giummarra and D. Darby served as study investigators, interviewed research subjects, collected data and assisted study design and article revision. M. Mastwyk supervised data collection, selected psychometric assessment tools and assisted study design and article revision. J. Robertson and C. Masters assisted study design and article revision. C. Rowe served as principal investigator, designed the study, obtained ethics approval, acquired funding and assisted article revision.

Trial registration

The clinical trial was registered both at www.anzctr.org.au and at www.trialadviser.com

[1]This phrase is commonly attributed to the Hippocratic Oath but not explicitly contained within it [50].

Disclosures

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ADDRESS FOR CORRESPONDENCE:

Carl Taswell, Brain Health Alliance, 8 Gilly Flower St, Ladera Ranch, CA 92694 USA, Tel: 1(949)481-3121; E-mail: ctaswell@BrainHealthAlliance.org