Movement Disorders
Vol. 25, No. 7, 2010, pp. 838–845

Anxiety Disorders in Parkinson's Disease: Prevalence and Risk Factors

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Abstract: Anxiety disorders are common in Parkinson's disease (PD) patients, yet are poorly studied. We examined the prevalence of anxiety disorders in PD, investigated the association between anxiety, and presentation and progression of PD, and studied for the first time the contribution of putative risk factors for anxiety in PD. A case-series of 79 PD patients recruited from neurology out-patient clinics was examined for anxiety disorders using the DSM-IV criteria. The Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr Staging of PD were employed to understand the relationship between anxiety disorders, and the clinical presentation and severity of PD. A validated survey assessed putative risk factors for anxiety in PD. Twenty-five percent of PD patients were diagnosed with anxiety. Panic disorder, generalised anxiety disorder and social phobia were prevalent anxiety disorders. Comorbid depression with anxiety was observed (14%). The severity but not the duration of PD was positively related to anxiety. PD patients with postural instability and gait dysfunction symptom clustering were more likely to experience anxiety than tremor-dominant patients. While levodopa dosage had no relationship to anxiety, experience of dyskinesias or on/off fluctuations increased the risk. Lateralisation of PD had no association with anxiety. Anxiety disorders decreased with age and young onset PD patients were more likely to experience anxiety than the late onset subjects. Anxiety adds to the complexity of PD, lowering patients' quality of life. Future research can be directed to identify reactive and organic nature of anxiety in PD. © 2010 Movement Disorder Society

Key words: prevalence; risk factors; Parkinson's disease; anxiety; depression

INTRODUCTION

Anxiety is a prevalent nonmotor symptom of Parkinson's disease (PD). Anxiety disorders complicate clinical diagnosis and treatment of PD, yet studies examining anxiety in PD are limited. The reported prevalence of anxiety disorders in PD varies greatly with estimates ranging from 3.6% to 40%.[1,2] Panic disorder, generalised anxiety disorder (GAD) and social phobia are the most common anxiety disorders reported. Anxiety and depressive disorders often coexist in PD and may precede motor symptoms.[3–5]

The relationship between anxiety and the severity of PD remains unclear. Two studies revealed no significant relationship between anxiety and severity of motor symptoms,[4,6] while one has shown an association with increased subjective motor symptoms.[7] Some have also suggested that anxiety disorders are associated with gait dysfunction and freezing in PD.[8–10] High anxiety levels have been observed in patients experiencing complications of pharmcotherapy such as dyskinesias or on/off fluctuations.[11,12] Fleminger[13] showed an association between anxiety and left-sided PD. Very few

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Potential conflict of interest: Nothing to report.
Received 22 May 2009; Accepted 19 September 2009
Published online 13 April 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22833

studies have comprehensively examined factors associated with anxiety in PD. Most of these isolated findings remain unreplicated and require further investigations. Moreover, there are no published studies focussing on the risk factors for anxiety disorders in the context of PD.

The aims of our study were as follows: To examine the prevalence of anxiety and depressive disorders in a case-series of PD patients; to investigate the relationship between anxiety disorders, and disease-related factors such as severity of motor symptoms, dominant motor symptom clustering, levodopa therapy, complications of pharmacotherapy and lateralisation of PD symptom onset; and to examine other putative risk factors associated with the presentation of anxiety in PD.

METHODS

Study Subjects

A consecutive series of PD patients was recruited from neurology out-patient clinics in Brisbane, Australia. All patients were diagnosed with idiopathic PD by movement disorders neurologists, according to the United Kingdom Brain Bank criteria.[14] Patients of Caucasian origin, who were able to complete the questionnaire and interviews by themselves or with assistance were included in the study. Patients who scored <24 in the Mini Mental State Examination[15] or responded affirmatively to the questions inquiring about a history of Alzheimer's disease and other dementias, were excluded from the study. Written informed consent was gained from all participants at the time of recruitment. This study was approved by the human research ethics committees at the participating institutions.

Examining the Prevalence of Anxiety and Depression in PD

A diagnosis of anxiety and depressive disorders was made using the Mini International Neuropsychiatric Interview plus version (MINI-plus).[16] The MINI-plus is a research tool that adheres to the DSM-IV criteria.[17] This study used an inclusive approach when recognising depressive and anxiety disorders with MINI-plus. Using this method all symptoms are taken into consideration regardless of whether they overlap between depression or anxiety, and PD. Such an inclusive approach has recently been recommended for studies examining depression in PD.[18] The spectrum of anxiety and depressive disorders screened by the MINI-plus are presented in Table 2. The frequency distributions of these disorders were examined. Anxiety defined as currently having an anxiety disorder including panic disorder, GAD, obsessive compulsive disorder (OCD) and social phobia was considered in subsequent analyses. The State version of the Speilberger State-Trait Anxiety Inventory (STAI)[19] was also applied to compare the anxiety levels between the anxious and nonanxious patient groups.

Examining the Relationship Between Anxiety and Severity of PD

The severity of PD was determined using the unified PD rating scale (UPDRS) sections II-activities of daily living (ADL) and III-motor examination, the Hoehn and Yahr staging and the Swab and England ADL score.[20] Relationships between current anxiety disorder and the onset age of PD, duration of PD, levodopa dosage and the experience of complications of PD therapy (dyskinesias or on/off effects) were also studied. Levodopa equivalent dosage calculations were made using a previously reported methodology.[21]

Examining the Relationship Between Anxiety and Presentation of PD

According to the UPDRS sections II and III, subjects were categorised into two groups of either tremor dominant or postural instability gait dysfunction (PIGD) patients following the method described by Jankovic et al.[22] The relationship between anxiety and these two forms of PD motor symptom clustering was examined. The association between the lateralisation of the first symptom onset and anxiety was also studied.

Investigating the Risk Factors for Anxiety in PD

Risk factor information was gathered using a telephone-interview survey developed by our group. This survey was based on a face-to-face-interview survey described by Gartner et al.[23] The telephone survey was applied by two interviewers. The test-retest repeatability and the inter-rater reliability of this survey were examined. Reproducibility measures of kappa values for categorical variables and interclass correlation coefficients for continuous variables were computed when investigating the repeatability and the inter-rater reliability of the risk factor questionnaire.

The association between current anxiety disorder and a number of factors were studied. Marital status was classified as either currently having or not having a life-partner. Exposure to pesticides and other chemicals, consumption of tea or coffee and smoking status

were studied. Regular exposure to pesticides was defined as "having personally used herbicides, fungicides or insecticides as a part of work or on a farm weekly for a period of 6 months or more." Tea and coffee drinkers were categorised as regular consumers verses others. Regular consumption was defined as "daily or nearly every day consumption for a year or more." Smoking status was described in pack years. One pack year is defined as the use of one packet (contains 20 cigarettes) daily for a year. History of hypertension, current depressive disorder (including major depression and dysthymia) and family-rated memory problems were also studied. Information on self and family history of psychiatric disorders was obtained from the Psychiatric History Screening questionnaire.[24]

Influence of Anxiety to Quality of Life in PD

The relationship between anxiety and quality of life was examined using the PD-specific quality of life questionnaire, PDQ-8.[25]

Statistical Analyses for Examining the Association Between Anxiety and Various Factors

Binary logistic regression models were constructed to examine the relationship between anxiety, and the factors of interest described above. A P-value of <0.05 was considered significant. All logistic regression models were adjusted for age and gender. *SPSS version 15.0* statistical package was used for all analyses.

RESULTS

One hundred and fourteen (114) subjects met the inclusion criteria. Seventy-nine PD patients (69%) completed the study. Twenty-one subjects did not consent to participate while 13 subjects could not be contacted via telephone. There were 42 males and 37 females in this study. No significant differences in age and gender were found between the participants and the nonparticipants. The patient characteristics of the study sample and the frequency distributions of the risk factors studied are presented in Table 1.

The prevalence of anxiety and depressive disorders found in this sample of PD patients is presented in Table 2. Twenty subjects (25%) had a diagnosis of a current anxiety disorder. The mean (SD) score of STAI for the anxious and nonanxious groups were 43.8 (14.7) and 30.3 (8.7), respectively ($P < 0.001$; t-test). The reliability of the telephone-interview risk-factor survey is presented in Table 3. The repeatability of this survey was examined within a time-frame of 6 months using 20 PD subjects randomly selected from the study sample. The inter-rater reliability was investigated using 10 PD subjects. The majority of questions showed high reproducibility and inter-rater reliability.

TABLE 1. *Patient characteristics and frequency distributions*

Variable	Mean (SD) or frequency
Age (yr)	67.2 (10.5)
Age <62 yr	25%
Gender (M/F)	42/37
MMSE	28.4 (1.7)
UPDRS-II-ADL score	14.5 (7.2)
UPDRS-III-Motor score	25.3 (11.2)
Hoehn and Yahr staging	
Mild (stages 1, 1.5 and 2)/moderate (2.5 and 3)/severe (4 and 5)	31/40/7
Schwab and England score	76.0 (15.0)
Duration of PD (yr)	8.2 (6.4)
Mean onset age (yr)	59.3 (12.2)
Onset age <61 yr	53%
Mean levodopa dosage (mg)	661.6 (460.6)
Complications of therapy	
Experiencing dyskinesias or 'on/off' effects (%)	55
Side of PD onset left/right/bilateral (%)	33/50/17
Presentation of PD	
Tremor dominant/PIGD[a]/mixed (%)	19/61/20
Have had surgery for PD (%)	15
PDQ-8 (quality of life measure)	3.2 (2.4)
Cigarette smoking (pack yr)	9.1 (15.9)
Ever smoked (%)	41
Regular tea drinkers (%)	76
Regular coffee drinkers (%)	77
Regular exposure to pesticides	
Personally using pesticides as a part of work or on a farm, weekly for 6 mo or more (%)	10
Pesticide dose (No. days)	19.5 (90.6)
Ever exposure to other chemicals (%)	27
Having memory problems (%)	6
Ever had hypertension (%)	40
Not having a life partner (%)	22
Self history of psychiatric disorders[b] (%)	37 (N = 29)
Depression (%)	37 (N = 28)
Schizophrenia/bipolar disorder/obsessive compulsive disorder	None
Panic disorder (%)	3 (N = 2)
Generalised anxiety disorder (%)	6 (N = 5)
Family history of psychiatric disorders[b] (%)	9 (N = 7)
Depression (%)	6 (N = 5)
Schizophrenia/bipolar disorder/obsessive compulsive disorder	None
Panic disorder (%)	3 (N = 2)
Generalised anxiety disorder (%)	3 (N = 2)

[a]Postural instability and gait dysfunction.
[b]Information obtained from the Psychiatric History Screening questionnaire.

TABLE 2. *Prevalence of anxiety and depressive disorders in Parkinson's disease*

Affective disorder	Frequency (%) (N)
Anxiety	
Current anxiety disorder	25 (20)
Current panic disorder (all with agoraphobia)	8 (6)
Previous panic disorder (if not met a current panic disorder)	10 (8)
Panic disorder with limited symptoms	1 (1)
Social phobia	13 (10)
Generalised anxiety disorder (in absense of other mental disorders)	3 (2)
OCD	1 (1)
Depression	
Current major depression	11 (9)
Current major depression with melancholia	10 (8)
Previous major depression	15 (12)
Current dythymia	6 (5)
Previous dysthymia	3 (2)
Suicidality	4 (3)
Current depression (current major depression, dysthymia or suicidality)	19 (15)
Current minor depression	6 (5)
Previous minor depression	4 (3)
Mixed anxiety and depression (if not met the criteria for major depression, dysthymia or any of the anxiety disorders)	1 (1)
Anxiety and depression	
Current anxiety disorder or depression (major depression or dysthymia)	29 (23)
Current anxiety disorder and depression (major depression or dysthymia)	14 (11)
Ever having any type of depression or anxiety disorder	46 (36)
Current panic disorder and major depression	4 (3)
Current panic disorder and dysthymia	0
Social phobia and major depression	5 (4)
Social phobia and dysthymia	3 (2)
OCD and major depression	1 (1)
OCD and dysthymia	0

OCD, obsessive compulsive disorder.

Our results revealed that severity of PD symptoms (as reflected in the highly correlated UPDRS scores, Hoehn and Yahr staging and Swab and England scores) was associated with the presence of anxiety (Table 4). The presence of treatment complications such as on/off fluctuations or dyskinesias was also associated with anxiety. Anxiety disorders contributed to a poor quality of life. Age was significantly associated with anxiety; dichotomising subjects according to the median age of 62 years showed that younger patients were more likely to experience anxiety disorder. A multivariate regression model was constructed to investigate whether this relationship was true when adjusted for age, severity of motor disability (the UPDRS-III-Motor score) and duration of the disease; results suggested that subjects <62 years were at almost ninefold increased risk for anxiety disorder compared with the older subjects (OR = 8.73, 95% CI = 2.18–34.94, $P = 0.002$). Moreover a marginally significant relationship was observed between the PIGD dominant symptoms of PD patients and anxiety disorders; with PIGD patients three-times more likely to present with anxiety (OR = 3.13, 95% CI = 0.92–10.66, $P = 0.07$). No significant association was observed between patients who had functional neurosurgery for PD and anxiety. History of psychiatric disturbances increased the risk for a diagnosis of current anxiety (OR = 4.78, 95% CI = 1.53–14.94, $P = 0.007$).

DISCUSSION

In our case series of PD subjects, 25% fulfilled the criteria for a current anxiety disorder. This was much higher than the prevalence reported in epidemiological studies focussing on non-PD subjects in Australia and

TABLE 3. *Reproducibility of the risk factor information obtained using the telephone-interview survey*

Description of the question	Repeatability	Inter-rater reliability
	Kappa (SD)/ICC (95% CI)	
Age	1.00	1.00
Father's ancestry (Caucasian = 1; other = 2)	1.00	1.00
Mother's ancestry (Caucasian = 1; other = 2)	1.00	1.00
Year of diagnosis	0.98 (0.94–0.99)	0.99 (0.94–0.99)
Year of symptom onset	0.92 (0.80–0.95)	0.99 (0.94–0.99)
Lateralisation (left = 1; right = 2; both = 0)	0.56 (0.19)	0.51 (0.23)
Functional neurosurgery (DBS = 1; Lesional = 2; None = 0)	0.88 (0.12)	1.00
Pesticides	1.00	1.00
Duration	0.98 (0.96–0.99)	1.00
Frequency (No. mo)	1.00	1.00
Other chemicals/toxins	0.83 (0.17)	1.00
Tea	0.78 (0.14)	1.00
Coffee	0.69 (0.21)	0.38 (0.36)
Tobacco	0.79 (0.14)	0.80 (0.19)
Duration	0.97 (0.93–0.99)	0.96 (0.86–0.99)
Amount per day	0.90 (0.75–0.96)	0.91 (0.68–0.98)
Hypertension	0.90 (0.10)	1.00
Family rated memory impairment	0.83 (0.17)	Incalculable[a]

The agreement for kappa or interclass correlation coefficient (ICC) values are; excellent ≥0.75, good = 0.4–0.75, and poor ≤0.4.

[a]Cannot be calculated due to small sample size.

TABLE 4. *Influence of the examined factors to anxiety in Parkinson's disease*

Variable[a]	Odds ratio (95% CI)	*P*
Age of <62 yr[b,c]	4.20 (1.34–13.21)	0.01
Higher UPDRS-II-ADL score[c]	1.19 (1.07–1.32)	0.001
Higher UPDRS-III-Motor score[c]	1.07 (1.01–1.13)	0.02
Moderate Hoehn and Yahr staging[c]	6.09 (1.40–26.48)	0.02
Severe Hoehn and Yahr staging[c]	10.75 (1.36–85.08)	0.02
Higher swab and England score[c]	0.95 (0.92–0.99)	0.02
Experiencing dyskinesias or motor fluctuations[c]	4.92 (1.38–17.57)	0.01
Higher levodopa dose	1.00 (1.00–1.00)	0.23
PD onset age of <61yr[c]	4.31 (0.99–18.79)	0.05
Longer duration of PD	0.98 (0.90–1.08)	0.73
Right sided symptom onset of PD	0.41 (0.12–1.46)	0.17
Left sided symptom onset of PD	1.42 (0.44–4.54)	0.56
Tremor dominant PD	0.61 (0.14–2.63)	0.50
PIGD[d] PD	3.13 (0.92–10.66)	0.07
Have had functional neurosurgery for PD	1.15 (0.29–4.63)	0.84
Higher PDQ8 score[c]	1.57 (1.21–2.03)	0.001
Cigarette smoking (pack years)	1.00 (0.97–1.03)	0.95
Ever smoked	1.03 (0.33–3.26)	0.96
Regular tea drinkers	1.67 (0.46–6.11)	0.43
Regular coffee drinkers	2.17 (0.51–9.27)	0.29
Regular exposure to pesticides	1.25 (0.24–6.43)	0.79
Ever exposure to other chemicals	1.19 (0.36–3.96)	0.78
Having memory problems	2.56 (0.37–17.83)	0.34
Ever had hypertension	1.21 (0.37–3.91)	0.75
Not having a life partner	1.32 (0.34–5.02)	0.69
Self history of psychiatric disturbances[c]	4.78 (1.53–14.94)	0.007
Family history of psychiatric disturbances	3.51 (0.61–20.20)	0.16

[a]All variables (except age) were examined in univariate logistic regression models adjusted for age and gender.
[b]A regression model was computed adjusting for gender and duration of Parkinson's disease.
[c]Significantly associated with anxiety at $P < 0.05$.
[d]Postural instability and gait dysfunction.

elsewhere.[26–28] These previous studies have reported an average anxiety prevalence of 10% in the general elderly community. Consistent with previously reported prevalence rates of anxiety disorders in PD,[4,5,29] we showed that anxiety disturbances are common in PD. This highlighted the importance of studying anxiety in PD and suggested the need for identifying anxiety symptoms when treating PD patients.

Panic disorder, GAD and social phobia were prevalent anxiety syndromes found in our Australian PD sample and this was consistent with the previously reported spectrum of anxiety disorders observed in PD. Ten percent (10%) of our PD patients experienced current panic disorder and this was slightly lower than the prevalence of current panic disorders previously observed in PD samples elsewhere (13% to 30%).[5,6,9,10,30] The reported prevalence of GAD in PD ranges widely from 0% to 40%;[5,6,9,31] our estimate was 3% in Australian PD subjects. While 15% (N = 12) of our PD patients showed symptoms of GAD, eight of these patients also experienced another comorbid depression and/or anxiety disorder, and as such could not be given a strict diagnosis of GAD. Thus the diagnosis of GAD in this sample was 3% (n = 2). Our finding of the prevalence of social phobia is similar to the only other study reporting the prevalence of social phobia in PD.[6] OCD was less prevalent in our PD sample (1%). Generally, OCD is not thought to be over-represented in PD compared to non-PD subjects.[5,32–34]

As expected, depressive syndromes coexisted with anxiety disturbances. The level of comorbidity between anxiety and depressive disorders found in our study was slightly lower than that reported by Menza et al.[4] (N = 42) and Nuti et al.[5] (N = 90). We reported that 14% of our PD subjects had a diagnosis of a comorbid depressive disorder with anxiety. Menza et al reported 26% comorbidity while Nuti et al reported 19% comorbidity. These two studies also reported higher frequency of anxiety disorders, generally, and this may account for the disparity in comparison to our sample.

We also studied the factors associated with anxiety disorders in PD and showed that anxiety disorders were related to more severe PD and to poor ADL. It was unclear whether decrease in ADL elevated the risk for anxiety or anxiety resulted in lowering ADL or both were due to a third factor. The PDQ-8 scores suggested that anxiety was related to a poor quality of life and was similar to observations reported in a prior study.[35] Experience of dyskinesias or on/off fluctuations showed positive associations with anxiety, while levodopa dosage had no effect. These results were also consistent with previous studies.[2] We did not study the psychological factors that might be associated with developing anxiety in PD and was a limitation of this study. For example PD patients could develop anxiety as a result of failed attempts at coping with a challenging illness, including anxiety related to the uncertainty of on/off phenomena. This may also account for the positive relationship between anxiety disorders and PD severity. Future study could be focussed on identifying psychological factors associated with anxiety disorders in PD with the view of directing PD patients towards better coping strategies, thus improving their quality of life.

We did not replicate the findings by Fleminger[13] suggesting that left sided PD is associated with higher anxiety implicating a potential right-sided involvement of the brain. Our study showed no relationship between anxiety disorders and the lateralisation of PD onset.

Interestingly, we observed that PD patients with a PIGD dominant symptom profile were more likely to experience anxiety than patients with the tremor dominant form. Gait dysfunction and freezing have been previously shown to associate with anxiety in PD.[8–10] It is worth noting that, in general, the PIGD symptom profile is associated with PD severity and in our study all seven patients with a Hoehn Yahr stage of >3 were classified in the PIGD group. Moreover we observed that 61% of our case series of patients was of PIGD dominant. This is consistent with the proportion of PIGD dominant patients (60%) in our much larger sample of Queensland PD patients consecutively recruited into the Queensland Parkinson's Project.[36] This proportion is somewhat higher than that previously reported large cohort study by Jankovic et al. (DATATOP study)[22] which consisted of PD patients with mild Hoehn and Yahr stage (stages 1 or 2).

We did not find any significant association between anxiety and duration of PD. However, PD subjects with a younger age of onset were more likely to have higher anxiety irrespective of their severity of PD motor symptoms. Anxiety disturbances also decreased with age. This is commonly seen in the general elderly samples.[28] None of the other risk factors examined showed associations with anxiety in PD. The use of a validated risk-factor research survey to obtain risk-factor information was a specific strength of our study and we were the first to examine such epidemiological markers for anxiety in PD. To avoid patient exhaustion of completing lengthy interviews, our risk-factor survey limited the number of factors examined. Aforementioned psychological factors, personality traits, life stressors and socioeconomic status are other factors of interest to study in future research.[37] Additionally genetic risk factors (for example, common genetic variations of the serotonin neurotransmitter transporter gene[38]) may also be of interest for future studies.

We used the currently available gold standard, DSM-IV criteria to diagnose the spectrum of anxiety disorders in PD. This was a specific strength of our study. It is recognised that screening anxiety in PD using rating scales available for research studies is complex and unreliable.[1] Well-validated methods to identify anxiety in PD for the research setting are needed. While focussing on identifying the phenotype of anxiety in PD, it is desirable to consider methods to identify past anxiety for particular use in risk-factor studies. Such studies require large sample sizes and investigating methods of identifying anxiety in a user-rated manner are also valuable. We limited our study sample to nondemented PD patients and thus, a majority of patients were of mild to moderate Hoehn and Yahr staging of PD. Further analysis will be required to examine the identification of anxiety in patients with more severe cognitive and movement symptoms.

In conclusion, for the first time, we showed the prevalence of anxiety disorders found in Australian PD patients. High rates of anxiety highlighted the need for recognition and treating anxiety disturbances in PD patients that can result in elevating their quality of life. Our study suggests that anxiety disturbances increase with the progression of PD. Factors associated with this positive relationship are unclear and warrant future research.

Acknowledgments: We thank Parkinson's Queensland Incorporated and late Mrs Olive Miles for providing financial support for this project. We thank Dr Richard Boyle at Princess Alexandra Hospital, Brisbane, Australia for assisting in patient recruitment and all patients of the study for their participation.

Financial Disclosures: Financial support for this project was received by a donation from Parkinson's Queensland Incorporated and late Mrs Olive Miles.

Dissanayaka, Sellbach, and Matheson have declared no financial disclosure in stock ownership in medically-related fields, consultancies, advisory boards, partnerships, honoraria, intellectual property rights, expert testimony, contracts, loyalities and others. Dissanayaka, N and Sellbach have declared no grants. Matheson was supported by grants from Royal Brisbane & Women's Hospital. Dissanayaka was employed as Clinical Research Officer, Department of Neurology, Royal Brisbane & Women's Hospital and as a Head demonstrator (casual), School of Biomedical Sciences, University of Queensland, Sellbach as Specialist registra in neurology, Oxford Radcliffe hospital trust, NHS, UK. Private practise and Matheson as Mental Health Centre, Royal Brisbane & Women's Hospital (20 hours/week), Medical legal report writing (4 hours/week).

O'Sullibvan, Silburn declared no stock ownership in medically-related fields, consultancies, partnerships, intellectual property rights, expert testimony, royalities and other. O'Sullivan was supported by grants from Royal Brisbane & Women's Hospital Foundation, Ipsen, and Hospira and Silburn from Australian National Health and Medical Research Council. O'Sullivan was a member of the advisory board of Hospira (Apomine), Novartis (Stalevo) and Solvay (Duodopa) and Silburn in Boehringer Ingelheim, Novartis and Medtronic. Honoraria was received from Hospira, Allergan, and Boehringer by O'Sullivan and from Medtronics by Silburn. O'Sullivan was employed as a senior visiting medical Officer at Royal Brisbane & Women's Hospital and Silburn involved in private practise at University of Queensland. Silburn has contract with Australian National Health and Medical research Council Principle Research Committee and Australian Health Ethics Committee.

Byrne, Marsh and Mellick declared no financial disclosure in stock Ownership in medically-related fields, consultancies, partnerships, contracts and others. Marsh declared no grants whereas Byrne was supported by grants from NHMRC ID 572563, Alz-

heimer's Association (U.S.) ID IIRG-07-59015, J.O. and J.R Wicking Trust [Gray, BYRNE, Jones, Martin-Khan, Morris, Pachana; Chenery, Humphreys, Hegney, Pachana, BYRNE, Gallois, Copland, Angwin], NHMRC ID 456182, RBWH Alzheimer's Disease Research Centre 2006–2008, NHMRC ID 511119, NHMRC ID 511125, NHMRC ID 511208. Mellick was supported by grants from Australian National Health and Medical Research Council. Byrne declared that "I expect to receive some royalties from commercial uses during the past year of the anxiety scale that I helped to develop, the Geriatric Anxiety Inventory. Commercial uses of the scale are being handled by Uniquest, the commerical arm of the University of Queensland. However, to my knowledge, none of these royalties have been received to date." Marsh and Mellick received no royalities. Byrne received honoraria from Novartis $550 for short lecture on the Rivastigmine transdermal patch; intellectual property rights from the University of Queensland, for curriculum materials and publications produced during his employment, no patents and this has been shared with his employer and expert testimony from Independent Expert for the Queensland Mental Health Court (Supreme Court) whereas Marsh and Mellick received none. Byrne is a member of the advisory board of Lundbeck (Memantine), Pfizer (Donepezil), and Janssen-Cilag (Galantamine & Risperidone). Byrne is employed by the employed by the University of Queensland & by the Royal Brisbane and Women's Hospital. He is a part-time member of the Australian Repatriation Medical Authority, a federal statutory body and also a part-time assisting psychiatrist on the Queensland Mental Health Court; Marsh has been employed as Consultant Psychiatrist at Royal Brisbane & Women's Hospital; and Mellick as Associate Professor, School of Biomolecular & Physical Sciences & Eskitis Insitute for Cell & Molecular Therapies, Griffith University.

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