Parkinsonism and Related Disorders 35 (2017) 25–29

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Delayed administration of dopaminergic drugs is not associated with prolonged length of stay of hospitalized patients with Parkinson's disease

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ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form
12 October 2016
Accepted 13 November 2016

Keywords:
Parkinson's disease
Medication
L-dopa
Delay
Length of stay

ABSTRACT

Background: Punctual delivery of dopaminergic medication to Parkinson's disease (PD) patients may be important in optimizing disease control. We tested the hypothesis that prompt delivery of L-dopa medications to emergency hospital inpatients was associated with a decreased length of stay in hospital.
Methods: The study population consisted of all urgent hospitalizations for patients with a diagnosis of PD to the Royal Derby Hospital over a two-year period. Data were extracted on timing of delivery of drugs, number of co-morbidities and length of stay. Statistical analysis used linear regression adjusting for within admission clustering.
Results: 431 individuals provided data from a total of 737 admissions. 39% of scheduled L-dopa doses were either not given or administered over 30 min later than the scheduled time. There was no association between the omission or timing of a dose of PD medication and length of stay in hospital. The number of coded diagnoses was strongly associated with length of stay with a dose-response association ($p_{TREND}<0.001$). Those with 10 concurrent diagnoses had a 11 day longer stay (95% confidence intervals: +2 to +21) than those with no comorbidities.
Conclusions: Delayed administration of dopaminergic drugs is not associated with prolonged length of stay of in patients with PD who were admitted to hospital as an emergency. However, the number of co-existing medical diagnoses was associated with length of stay, and early attention to these has the potential to improve patient care and decrease length of stay in hospital.

1. Introduction

People with Parkinson's Disease (PD) are one and half times more likely than others to be admitted to hospital, they stay longer and have more complications [1–3]. The cost of PD admissions in England is estimated to be more than £200 m per year and the number of hospitalizations is increasing [4,5]. Omission of dopaminergic medication, delays in administration of dopaminergic medication and inappropriate use of anti-dopaminergic medication commonly occur when Parkinson's disease patients are hospitalized [1,6–13]. Omission of dopaminergic medication is associated with worse motor performance both in hospital and in the community [14,15]. PD patients commonly report delays in getting their medication and one in four believe such delays lead to longer hospital stays [16,17].

A recent US study reported increased length of hospital stay in PD patients with at least one dose of PD medication that was omitted or delayed more than an hour. Administration of dopamine antagonists was also associated with increased length of stay [18]. We have recently completed a study into the impact of a specialist unit for the care of Parkinson's disease patients on a number of quality indicators [19]. A *post hoc* analysis of these data demonstrate that patients who received their Parkinson's medication late had a longer length of stay than those who received it promptly, and that 12% of the variation in length of stay was explained by timing of medication delivery.

We used data from the introduction of an electronic prescribing and administration system in a busy District General Hospital to

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http://dx.doi.org/10.1016/j.parkreldis.2016.11.004

explore the association between omissions and delays to administration of medications to in-patients with Parkinson's disease and their length of stay. We focused on L-dopa medications because of its short half life and repeated the analysis with dopamine agonists (ropinirole, rotigotine, pramipexole, apomorphine).

2. Methods

2.1. Study population

The study population consisted of all patients with a diagnosis of PD that were admitted to the Royal Derby Hospital from the period of 25th March 2012 to 31st March 2014 for at least one day and were subsequently discharged. The hospital patient administration system was used to identify cases with a primary or secondary diagnosis of PD. For these admissions, prescription data was extracted using an electronic prescription system (iCM, Isoft) and only those on dopaminergic or anti-dopaminergic medication were included in the study. Dopaminergic medications included in the study were: Levodopa (co-beneldopa, co-careldopa, Stalevo), dopamine agonists (ropinirole, rotigotine, pramipexole, apomorphine). Drugs that were regarded as contraindicated in the context of PD were: amisulpiride, chlorpromazine, haloperidol, levomepromazine, metoclopramide, olanzapine, prochlorperazine, promazine, risperidone and sulpiride. We used the hospital electronic prescribing system to extract the following data: age, sex, number of associated diagnoses at discharge, medications, scheduled medication administration time, actual medication administration time, omitted doses, reason for omission of medication, and length of stay. Self-medicating patients were excluded from the analysis. Ethical approval was not required as only routinely collected anonymised data was used.

2.2. Statistical analysis

Linear regression was used to explore the association of timeliness of delivery of L-dopa medication with length of stay. We defined late medication delivery as 30 min or more after scheduled delivery time or documented omission of the drug dose. Each drug administration was considered as one event and data from multiple time points for each individual's hospital admission were adjusted for using robust standard errors. This generated a measure of the association between an additional missed or omitted dose of medication and length of stay for each hospital admission period. Secondary analyses looked at: the association between timing of dopamine agonists and length of stay; the association between prescription of contraindicated dopamine antagonists with length of stay; the effect of weekends v weekdays on prompt delivery of PD medications. All analyses were adjusted for gender, age as a categorical variable and the number of recorded medical diagnoses. Sensitivity analyses were performed using a broader definition of late medication administration with a 60-min delay from scheduled time. We were unable to complete a stratified analysis by L-dopa dose frequency as 47% of the population has a personally designed drug regimen. All statistical analysis used Stata statistical software (v13, Texas).

3. Results

For the main analysis, data were available on a total of 737 admission episodes from a population of 431 individuals. Of these, the median age was 82 years (interquartile range 77–87, Fig. 1) and 236 (55%) were male. The median number of coded co-morbidities was 7 (interquartile range 5–10). The median length of stay for all admissions was 8 days (interquartile range 4–17, Fig. 2).

29587 doses of L-dopa were prescribed over the study period. Of these doses, 11382 (38.75%) were delayed (omitted or administered more than 30 min later than the scheduled time). For those who received their L-dopa, the median difference for administering any of this medication was +9 min (interquartile range IQR: −16 to +41) after the scheduled time. 2848 (9.7%) doses had documented omission codes. Main reasons for omission of medication were as follows: medicine not available, 554 doses (19%); medicine refused by patient 322 doses (11%); patient nil by mouth 309 (11%); route not available 238 doses (8%). Also see supplementary table online.

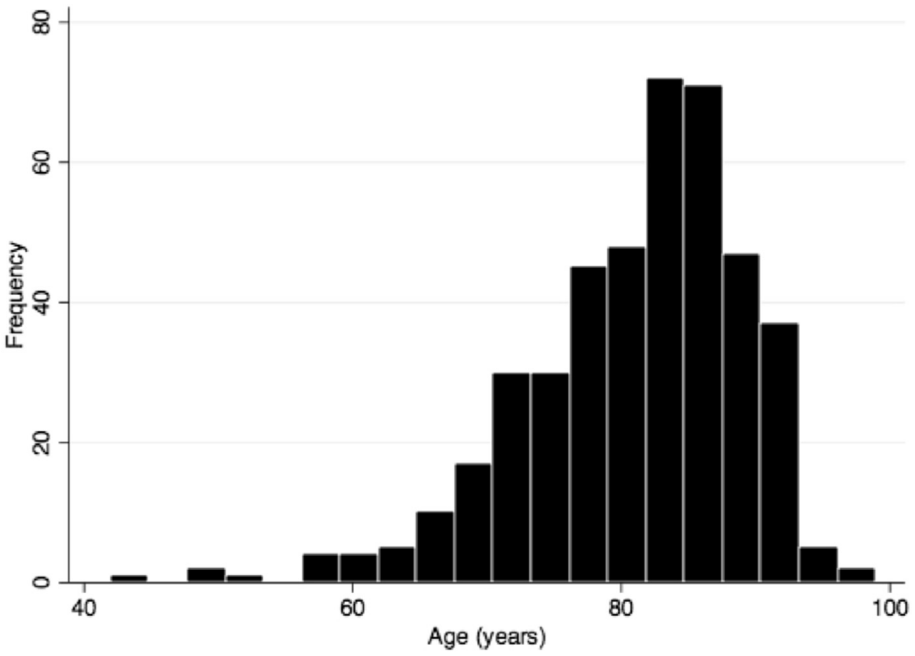

Fig. 1. Age of study population.

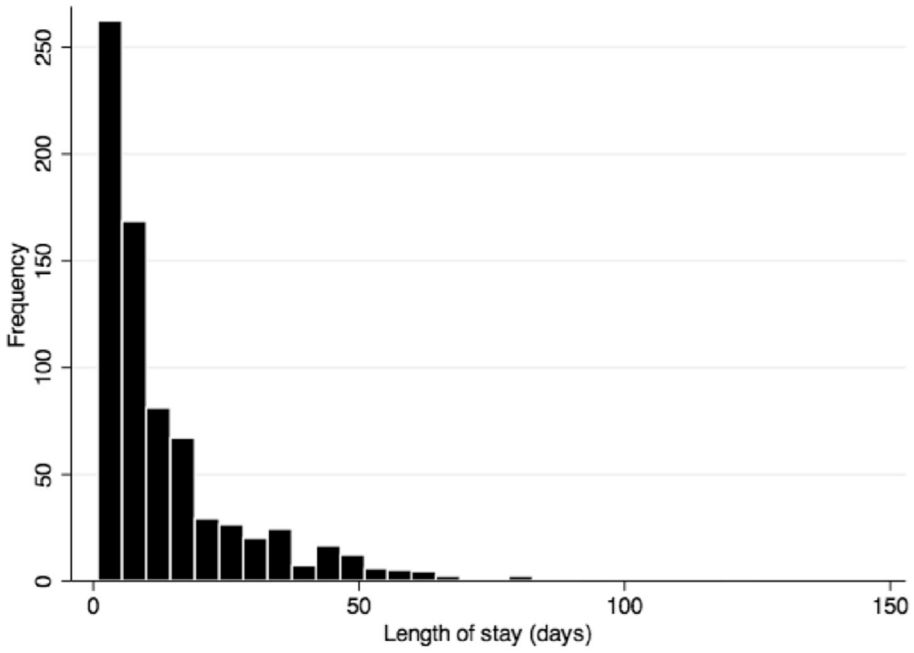

Fig. 2. Length of stay in hospital for study population.

In the primary multivariate analysis (Table 1), there was no association between the number of late or omitted L-dopa drug administrations and length of stay in hospital after adjusting for confounding factors. Sensitivity analyses redefining late medication as omitted or delayed more than 60 min (N = 7060 doses, 24%) similarly demonstrated no association with length of stay. The presence of a weekend made no difference to the lateness of delivery of L-dopa compared to weekdays (data not presented).

Table 1
Multivariate model of association of delay in administration timing of L-dopa[a] with length of stay in hospital adjusting for sex, age and number of co-morbidities.

	No. of dose (%)	Length of stay, days (95% CI)
Drug given late (>30 min or omitted)		
Yes	11382 (39)	−0.88 (−2.51 to +0.75)
No	18005 (61)	0
	No. of individuals (%)	
Age		
<69	41 (10)	0
70–79	108 (25)	−10.29 (−26.56 to +5.98)
80–89	225 (52)	−10.92 (−26.20 to +4.37)
90+	57 (13)	−13.16 (−28.55 to +2.24)
Sex		
Female	195 (45)	0
Male	236 (55)	−0.18 (−5.36 to +5.00)
Number of co-morbidities		
1	3 (1)	0
2	11 (3)	−12.87 (−24.93 to −0.82)
3	29 (7)	−5.31 (−14.57 to +3.96)
4	45 (10)	+4.91 (−7.87 to +17.69)
5	45 (10)	+7.64 (−3.34 to +18.62)
6	58 (13)	+8.48 (−2.15 to +19.12)
7	57 (13)	+7.02 (−4.06 to +18.11)
8	39 (9)	+10.90 (+1.57 to +20.23)
9	36 (8)	+17.83 (+3.88 to 31.77)
10	33 (8)	+10.56 (+1.44 to 19.67)
11	75 (17)	+22.47 (+12.29 to +32.65)
	p_{TREND}<0.001	

CI = confidence intervals.
Analysis used linear regression adjusted clustering by each patient's hospital visit.
[a] Co-beneldopa/co-careldopa/Stalevo.

Similarly, delayed administration (defined as >30 min) or omission of dopamine agonists (apomorphine, premipexole, ropinirole, rototigine) was not associated with length of stay in hospital after adjusting for confounding factors.

40 (9%) patients out of a total population of 431 patients with a diagnosis of PD received contraindicated drugs. Administration of contraindicated dopamine antagonists was not associated with increased length of stay after adjustment for sex, age and number of other diagnoses (Table 2). Similarly, those who received allowed antipsychotic drugs or anti-dementia medication did not have a longer length of stay.

The number of coded diagnoses was strongly associated with length of stay (p_{TREND} <0.001). There was a dose-response association and those with 10 concurrent diagnoses had a 11 day longer stay (95% confidence intervals: +2 to 21) than those with no comorbidities.

4. Discussion

The study is the first to use an electronic prescribing system to

Table 2
Association of other prescribed drugs with length of stay in a population of patients admitted with Parkinson's Disease.

	No. of medication episodes (%)	Length of stay (95% CI)
Contra-indicated drugs[a]		
Yes	1167 (4)	−2.58 (−11.11 to +5.95)
No	29387 (96)	–
Allowed antipsychotic medication[b]		
Yes	1302 (4)	+2.51 (−2.11 to +7.13)
No	30657 (96)	–
Anti-dementia medication[c]		
Yes	2879 (9)	−1.23 (−5.43 to +2.97)
No	30657 (91)	–

Linear regression model adjusted for sex, age and number of concurrent co-morbidities.
[a] Amisulpiride, chlorpromazine, haloperidol, metaclopramide, olazanepine, prochlorperazine, promazine, risperidone.
[b] Clozapine, Quetiapine.
[c] Donepazil, Galantamine, Memantine, Rivastigmine.

explore the association between timing of dopaminergic medication with length of stay in a population of patients with Parkinson's disease. The results demonstrate 39% of L-dopa medication is given late or not at all. However, after adjustment is made for age, sex and the number of co-morbidities, the timing of L-dopa administration is not associated with the length of stay in hospital. The number of co-morbidities is however strongly associated with length of stay even after adjusting for age, and this has important implications for providing appropriate medical care for these patients.

The strengths of these data include the fact that it is the largest study to date looking at the impact of timing of delivery of Parkinson's medication in this patient group. The data were collected using the electronic prescribing system that permits accurate measurement of the timing of the delivery of medication, and comparison with the prescribed time. We were also able to explore the impact of the prescription of medications that are generally contraindicated in patients with PD. The electronic data collection system allowed adjustment for the number of discharge diagnoses for each patient, as well as age and sex, and the association of these covariates with length of hospital stay as well.

These analyses do have a number of limitations. Firstly, the pragmatic use of coding diagnoses of PD rather than application of strict diagnostic criteria such as the UK Brain Bank Criteria was necessary to identify all eligible patients. However, in the primary analysis all patients in our study were on dopaminergic medication so we are confident that it is very likely that these patients had a diagnosis of PD. Secondly, these data are from a single centre and may not be representative of standard practice elsewhere. Thirdly, we have used a number of statistical analyses on these data, so are unable to exclude the possibility of a false positive test as a consequence of multiple hypothesis testing. Unfortunately, we did not have an accessible measure of disease severity. Clearly if most individuals had early stage Parkinson's without wearing off symptoms, then missed or delayed doses might be well tolerated. Similarly, the use of electronic diagnostic coding data limits our ability to distinguish between admissions that are directly a consequence of PD, and those due to an unrelated diagnosis. Also the coding data did not allow consideration of other potentially important confounding factors such as place of residence and cognitive function. Finally, the choice of length of stay was an opportunistic outcome measure, and the use of a quality of life measure or evaluation of control of Parkinson's symptoms while in hospital would better reflect patients' priorities.

Our use of linear regression for the statistical analysis was selected to allow us to test if the hypothesis that delayed PD drug administration resulted in increased length of stay. The 95% confidence intervals will necessarily span zero if the exposure of interest was not significantly associated with the outcome, creating a negative length of stay which represents a p value greater than 0.05. We initially aimed to stratify the analysis by drug frequency, but were unable to do so as 47% of the population has a medication regimen tailored to their clinical needs. As a consequence, we were unable to explore the associations of frequency of PD medications with length of stay any further. In the context of a clear rejection of the hypothesis being tested, we did not proceed to any further analysis looking at L-dopa equivalent doses [7].

It is important to consider why the timing of delivery of Parkinson's medications is not associated with length of stay, as this is clearly important to patients and their families [7,16], recognized by clinicians as an important factor in improving control of PD [14] and others have reported that it is associated with decreased length of stay [18]. Firstly, we studied a population of patients with a diagnosis of PD who were admitted as emergency admissions to hospital. Clearly, this is a very heterogeneous group with a range of medical and surgical reasons for admission, and, Parkinson's Disease was often a documented co-morbidity rather than the primary diagnosis. This is opposed to a population of patients who are admitted with a primary problem associated with Parkinson's disease where choice and timing of medication, as well as other interventions such as physiotherapy are clearly essential. The absence of any association between timing of Parkinson's medications and length of stay certainly does not make this issue any less of a priority in the care of this patient group. Secondly, prompt administration of medication may only be important for those with wearing off symptoms and/or motor fluctuations. Thirdly, some patients, for example those with delirium, may have benefited from the reduced dopaminergic stimulation associated with missed medication [20].

While it is well recognized by physicians that clinical deterioration can be associated with delayed delivery of medications and initiation of anti-psychotic drugs, we are unable to demonstrate this in our dataset. Only 9% of the patients had contraindicated antipsychotic medication and we were unable to distinguish between established antipsychotic medication and new prescriptions.

In a study of hospitalizations of people with Parkinson's, Ramirez-Martinez et al. report that participants who had delayed or missed at least one dose stayed in the hospital for longer (median 5 days) compared to those who did not (median 2 days) [18]. That study differed from our study: most prescriptions specified a frequency rather than a precise time. Also it is not clear to us if there was any statistical adjustment for the number of scheduled doses, as clearly with longer periods of time spent in hospital the probability of missed medication increases as a consequence of increased exposure.

The most striking observation in these analyses is the very strong dose-response association between the number of coded diagnoses on discharge from hospital with length of stay even after adjustment for age. Although we are unable to distinguish between new diagnoses acquired during the hospital admission in question and pre-existing diagnoses, this has large implications for the care of people with Parkinson's admitted to hospital as geriatricians and general internists used to managing multiple conditions may be at least as important in caring for such people as movement disorder experts. Geriatric liaison services in orthopaedics and in perioperative care appear to improve care and may do so for the hospitalized Parkinson's patient [21].

In summary we found no association between omitted and delayed dopaminergic medication with length of hospital stay. Many of those with Parkinson's admitted to hospital were elderly and the number of coded diagnoses was strongly associated with length of stay. This is an obvious but important area where better geriatric liaison services might have the potential to improve care for the hospitalized Parkinson's patient.

Funding

This work was supported by Parkinson's UK [Grant number K-1402].

Acknowledgements

We also acknowledge the generous and patient assistance of Helen Staniforth who extracted data from the hospital's electronic prescription and medicines administration system.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.11.004.

References

[1] O.H.H. Gerlach, A. Winogrodzka, W.E.J. Weber, Clinical problems in the hospitalised Parkinson's Disease patient: systematic review, Mov. Disord. 26 (2011) 197–208.

[2] M. Guttman, P.M. Slaughter, M.-E. Theriault, D.P. DeBoer, C.D. Naylor, Parkinsonism in Ontario: comorbidity associated with hospitalization in a large cohort, Mov. Disord. 19 (2004) 45–53.

[3] P. Pepper, M. Goldstein, Postoperative complications in Parkinson's disease, J. Am. Geriatr. Soc. 47 (1999) 967–972.

[4] V. Low, Y. Ben-Shlomo, E. Coward, S. Fletcher, R. Walker, C.E. Clarke, Measuring the burden and mortality of hospitalization in Parkinson's Disease: a cross-sectional analysis of English Hospital Episodes Statistics database 2009-2013, Park. Relat. Disord. 21 (2015) 449–454, http://dx.doi.org/10.1016/j.parkreldis.2015.01.017.

[5] Department of Health, Services for People with Neurological Conditions, National Audit Office, London, UK, 2011. https://www.nao.org.uk/wp-content/uploads/2011/12/10121586.pdf.

[6] K.N. Magdalinou, A. Martin, B. Kessel, Prescribing medications in Parkinson's disease (PD) patients during acute admissions to a District General Hospital, Park. Relat. Disord. 13 (2007) 539–540.

[7] O.H.H. Gerlach, M.P. Broen, P.H. van Domburg, A.J. Vermeij, W.E. Weber, Deterioration of Parkinson's disease during hospitalization: survey of 684 patients, BMC Neurol. 12 (2012) 13, http://dx.doi.org/10.1186/1471-2377-12-13.

[8] P.C. Derry, K.J. Shah, L. Caie, C.E. Counsell, Medication management in people with Parkinson's disease during surgical admissions, Postgrad. Med. J. 86 (2010) 334–337, http://dx.doi.org/10.1136/pgmj.2009.080432.

[9] J.G. Hou, L.J. Wu, S. Moore, C. Ward, M. York, F. Atassi, L. Fincher, N. Nelson, A. Sarwar, E.C. Lai, Assessment of appropriate medication administration for hospitalized patients with Parkinson's disease, Park. Relat. Disord. 18 (2012) 377–381.

[10] L.C. Tan, A.K. Tan, H.T. Tjia, The Profile of Hospitalised Patients with Parkinson's Disease vol. 27, Annals of the Academy of Medicine, Singapore, 1998, pp. 808–812.

[11] S. Domingo-Echaburu, U. Lertxundi, E. Gonzalo-Olazabal, J. Peral-Aguirregoitia, I. Pena-Bandres, Inappropriate antidopaminergic drug use in Parkinson's Disease inpatients, Curr. Drug Ther. 7 (2012) 164–169.

[12] K.L. Chou, J. Zamudio, P. Schmidt, C.C. Price, S.A. Parashos, B.R. Bloem, K.E. Lyons, C.W. Christine, R. Pahwa, I. Bodis-Wollner, W.H. Oertel, O. Suchowersky, M.J. Aminoff, I.A. Malaty, J.H. Friedman, M.S. Okun, Hospitalization in Parkinson disease: a survey of national Parkinson foundation centres, Park. Relat. Disord. 17 (2011) 440–445.

[13] R. Skelly, L. Brown, A. Fakis, R. Walker, Hospitalization in Parkinson's disease: a survey of UK neurologists, geriatricians and Parkinson's disease nurse specialists, Park. Relat. Disord. 21 (2015) 277–281.

[14] O.H.H. Gerlach, M.P.G. Broen, W.E.J. Weber, Motor outcomes during hospitalization in Parkinson's disease patients: a prospective study, Park. Relat. Disord. 19 (2013) 737–741.

[15] D. Grosset, A. Antonini, M. Canesi, G. Pezzoli, A. Lees, K. Shaw, E. Cubo, P. Martinez-Martin, O. Rascol, L. Negre-Pages, A. Senard, J. Schwarz, K. Strecker, H. Reichmann, A. Storch, M. Löhle, F. Stocchi, K. Grosset, Adherence to antiparkinson medication in a multicenter European study, Mov. Disord. 24 (2009) 826–832.

[16] M. Barber, D. Stewart, D. Grosset, G. MacPhee, Patient and carer perception of the management of Parkinson's Disease after surgery, Age Ageing 30 (2001) 171–172.

[17] Parkinson's Disease Society, Life with Parkinson's Today - Room for Improvement, 2008. Report, https://www.parkinsons.org.uk/sites/default/files/publications/download/english/memberssurvey_fullreport.pdf.

[18] D. Martinez-Ramirez, J.C. Giugni, C.S. Little, J.P. Chapman, B. Ahmed, E. Monari, A.W. Shukla, C.W. Hess, M.S. Okun, Missing dosages and neuroleptic usage may prolong length of stay in hospitalized Parkinson's disease patients, PLoS ONE 10 (2015) e0124356, http://dx.doi.org/10.1371/journal.pone.0124356.

[19] R. Skelly, L. Brown, A. Fakis, L. Kimber, C. Downes, F. Lindop, C. Johnson, C. Bartliff, N. Bajaj, Does a specialist unit improve outcomes for hospitalized patients with Parkinson's Disease? Park. Relat. Disord. 20 (2014) 1242–1247, http://dx.doi.org/10.1016/j.parkreldis.2014.09.015.

[20] J.R. Maldonado, Neuropathogenesis of delirium: review of current etiologic theories and common pathways, Am. J. Geriat. Psychiatr. 21 (2013) 21, http://dx.doi.org/10.1016/j.jagp.2013.09.005, 1190–1222.

[21] B. Ozalp, T.J. Aspray, Orthogeriatric medicine and fracture liaison going from strength to strength, Age Ageing 45 (2016) 180–181, http://dx.doi.org/10.1093/ageing/afw008.