Specialist medication review does not benefit short-term outcomes and net costs in continuing-care patients

George Pope', Noreen Wall', Catherine Mary Peters', Margaret O'Connor', Jean Saunders', Catherine O'Sullivan', Teresa M. Donnelly', Thomas Walsh', Steven Jackson², Declan Lyons', David Clinch'

Address of the correspondence to: G. Pope. Tel: (+44) (0)7867 564117; fax: (+44) (0)1865 234815. Email: georgepopea@ gmail.com

Abstract

Objectives: to evaluate specialist geriatric input and medication review in patients in high-dependency continuing care.

Design: prospective, randomised, controlled trial. **Setting:** two residential continuing care hospitals.

Participants: two hundred and twenty-five permanent patients.

Intervention: patients were randomised to either specialist geriatric input or regular input. The specialist group had a medical assessment by a geriatrician and medication review by a multidisciplinary expert panel. Regular input consisted of review as required by a medical officer attached to each ward. Reassessment occurred after 6 months.

Results: one hundred and ten patients were randomised to specialist input and 115 to regular input. These were comparable for age, gender, dependency levels and cognition. After 6 months, the total number of medications per patient per day fell from 11.64 to 11.09 in the specialist group (P = 0.0364) and increased from 11.07 to 11.5 in the regular group (P = 0.094). There was no significant difference in mortality or frequency of acute hospital transfers (11 versus 6 in the specialist versus regular group, P = 0.213). Conclusion: specialist geriatric assessment and medication review in hospital continuing care resulted in a reduction in medication use, but at a significant cost. No benefits in hard clinical outcomes were demonstrated. However, qualitative benefits and lower costs may become evident over longer periods.

Keywords: hospital continuing care, geriatric medicine, long-term care, multidisciplinary team, medication review

Introduction

Medical care of frail older people is an increasing challenge for all Western health-care providers. Projected increases in longevity will almost certainly be accompanied by growth in the number of elderly patients with a concomitant requirement for continuing nursing care provision. The medical management of frail elderly patients is complex. For example, drug–patient and drug–drug interactions are more likely to produce deleterious effects in this population group [1–4].

There has been a growth in specialist geriatric medicine provision in both Europe and North America, largely based on the rise in the elderly population. To our knowledge, there has not been formal evaluation of hard outcomes of specialist geriatric medical assessment and medication review in the management of high-dependency patients in hospital continuing-care settings. This is despite the fact that such specialist input into these settings is being promoted by some health-care providers [5, 6]. In our facilities, standard care is provided by general practitioners but lacks a proactive input from a team of age-related specialists. This study provides a substantial input of such expertise.

Several studies have highlighted the prevalence of inappropriate prescribing in the elderly [1–4], along with the clinical and economic consequences [7–10]. Intuitively, one might expect improved outcomes from enhanced specialty input, particularly in relation to promoting rational drug prescribing. This should ensure early identification of

¹Mid Western Regional Hospital, Clinical Age Assessment Unit, Limerick, Ireland

²Kings College Hospital, London, UK

G. Pope et al.

adverse pharmacokinetic and pharmacodynamic drug interactions [11].

Tools including Beers, Inappropriate Prescribing in the Elderly, King's Criteria and Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) [12–16] have been developed as adjuncts to identify potentially inappropriate prescribing. In addition, pharmacist review of prescribing in elderly patients has been shown to reduce morbidity, falls and the number of medicines prescribed [17, 18]. Therefore, several methods are available, which try to assist in identifying suboptimal prescribing. To date, none have yielded benefits in long-term outcomes in the frailest elderly, namely those who reside in continuing care [16, 19].

To ascertain this, we conducted a prospective, randomised, controlled study comparing the impact of specialist input to regular input on major health outcomes in a dependent elderly patient population based in hospital continuing care. These outcomes included drug utilisation, mortality and requirement for transfer to acute hospital care.

Methods

This was a prospective, randomised, controlled study conducted over a period of 6 months. It was performed in 10 nurse-managed, continuing-care wards situated in two community hospitals (one urban; one rural 25 miles away). The regular medical input was provided by a medical officer (i.e. a general practitioner with a diploma in medicine for the elderly) as is the standard practice within these institutions. There was access to specialist geriatric medicine advice on request.

Prior to admission, the suitability of each patient for admission to a continuing-care ward had been assessed by a multidisciplinary panel chaired by a consultant geriatrician. This ensured that all remediable medical and rehabilitation potential had been fully maximised. Admission criteria for hospital continuing care are formulated to allow only patients of the highest dependency requiring expert nursing care to be accepted to these institutions.

Intervention

All permanent patients on the continuing-care wards were included in the study. They were allocated using a random number generator to either a regular or a specialist input. We felt that cluster randomisation of the wards or institutions would be inappropriate. Local practices produce significant differences between wards and institutions (i.e. different medical officers, consultant physicians, nursing staff along with varying institutional policies and practices. Significantly, more medically complex patients were clustered particularly in high dependency wards, with more mobile and cognitively impaired patients in other wards). Thus, with expert statistical advice, cluster randomisation seemed unsuitable, due to the major confounding factors described.

Demographic and other data were collected by the study nurse (N.W.) who was blind to all aspects of the study.

Patients in the specialist group were clinically assessed, by either a consultant or a senior specialist registrar in geriatric medicine, working in pairs. The drug prescription charts were then reviewed by the multidisciplinary panel. A series of evidence-based recommendations were forwarded to the general practitioner for consideration. There was no explicit direction or insistence that these recommendations be implemented. Compliance with recommendations was measured.

The multidisciplinary panel comprised three consultant geriatricians, six specialist registrars in geriatric medicine, two registered hospital pharmacists and three senior nurse practitioners. They had access to the complete medication list for all patients in the intervention group along with the details of a comprehensive medical assessment. Using this information, the team applied tools such as Beer's criteria, Inappropriate Prescribing in the Elderly Tool and the British National Formulary to aid the decision regarding medication use [12–15]. Ultimately, the decision to continue or discontinue a medication was made using a modified Delphi method [20]. Patients in the control group did not undergo specialist medical assessment or medication review by the multidisciplinary panel.

A dedicated database was constructed. This included patient demographics, previous medical history, a detailed medication list, functional, cognitive and dependency levels at the time of initial evaluation. The study pharmacist calculated daily medication costs.

Evaluation

The primary aim of the study was to assess the impact of specialist input compared with regular input on the number of drugs prescribed and medication cost over a 6-month period in a continuing-care setting. Secondary outcomes were the frequency and timing of requested medical officer reviews (daytime 09:00–17:00 or out-of-hours 17:00–09:00), number of emergency transfers to acute hospital care and mortality.

The costs for each group over 6 months were calculated on the basis of the price of the initial medical review, the panel review, medications administered, medical officer assessments and acute hospital transfers (based on cost of bed days utilised). The costing of medication was performed by a pharmacist, who was blinded to the groups.

Baseline Barthel Index (20-point score) and Abbreviated Mental Test Score (AMTS 10-point score) were recorded at 0 and 6 months by the same researcher.

Statistical analysis was performed with the assistance of an expert statistician, who was blinded to the groups, using SPSS 16.0 (Statistical Package for Social Sciences, Version 16). Parametric tests were used for normally distributed variables and non-parametric tests for non-normally distributed variables.

Specialist medication review in continuing care Thus, in the specialist input group, there was a significant formula of the patient relationship in the specialist input group, there was a significant formula of the patient relationship in the specialist input group, there was a significant formula of the patient relationship in the specialist input group, there was a significant formula of the patient relationship in the specialist input group there was a significant formula of the patient relationship in the specialist input group.

Informed consent was obtained from the patient, relatives or the director of nursing in each institution as appropriate, depending on the capacity of the patient to give informed consent. Further to discussion with the statistician, all patients from both institutions for whom consent was obtained were included, in order to maximise the power of the study. Ethical approval was obtained from the Ethics Committee of the Mid-Western Regional Hospital, Limerick. The trial protocol was registered on 19 January 2005.

Results

Two-hundred and twenty-five patients were eligible for inclusion in the study (110 in the specialist input group versus 115 in the regular input group). Baseline characteristics for both groups were similar, including age, level of care criteria (as assessed by placement panel prior to admission), gender, initial AMTS, Barthel Index and the total number of medications per patient per day (Table 1). The duration of time from admission to continuing care until review for this study was not significantly different (*post hoc* analysis on data available for 103 patients in the regular input group and 100 patients in specialist input group; Table 1). Follow-up data were available on all study patients at 6 months.

Medications

In the specialist input group, one or more medication changes were advised in 102 (92.7%) patients. The reasons put forward by the panel to discontinue medications included the lack of a clear indication for use, potential adverse effects or potential interactions. Also included was the panel's advice to recommend new medications in 83 patients (76%). Compliance with the suggested changes was audited, and in 80.1% of the patients, the advised changes were fully or partially implemented.

Thus, in the specialist input group, there was a significant reduction in the total number of medications and in the number of regular medications. Total medications in this group fell from 11.64 to 11.09 per patient per day (P = 0.0364) (95% CI for mean difference (-1.06, -0.04)). In the regular input group, the opposite was observed with an overall increase in total medications per patient per day from 11.07 to 11.5 (P = 0.094) (95% CI for mean difference (-0.07, 0.93). Adjusted mean difference and 95% CI: -0.88 (-1.57, -0.18).

Functional outcomes and mortality

At the end of the 6-month period, there was no change in the Barthel Index or AMTS between the groups. There was a higher rate of nursing requests for medical reviews in the specialist input group, 3.95 (4) mean (median) compared with 3.08 (2) in the regular input group (P = 0.07) using the non-parametric Mann-Whitney test. The mean difference plus 95% CI was -0.87 (-1.68, -0.05), P = 0.037, independent sample t-test. There was a higher rate of referral (non-significant) for acute hospital assessment in the specialist input group (11 versus 6, P = 0.213). Two patients in the specialist input group were admitted with possible medication-related side effects. One patient was admitted with gastritis, which may have been aggravated by a reduction in the proton pump inhibitor dose as recommended by the panel (Table 2). There was one subject in the control group admitted primarily due to medicationrelated adverse effects. Total length of stay was 101 days in the specialist input group and 63 days in the control group.

Mortality was not significantly higher in the specialist input group (17 versus 11, P = 0.226).

Costs

Overall, there was a net reduction in total medication costs of £19,753 (€20,972) over the 6 months of the study. This resulted from a reduction in medication costs in the

Table 1. Demographics and outcomes in both groups (statistical analysis in text)

	Control group (regular input, $n = 115$)	Study group (specialist input, $n = 110$)	
Mean age	82.5	83.3	
Gender: male:female	41:74	38:72	
Years in continuing care (median) ^a	2.36	3.19	
Barthel at Month 0 (mean/median)	6.75 (4)	5.95 (4)	
Barthel at Month 6 (mean/median)	6.62 (3)	5.94 (4)	
AMTS at Month 0 (mean/median)	4.2 (3)	4.2 (4)	
AMTS at Month 6 (mean/median)	4.2 (3)	4.1 (3)	
Deaths (total number)	11	17	P = 0.226
Number of admissions to acute hospital	6	11	P = 0.213
Number of medical officer reviews per patient (mean/median)	3.08 (2)	3.95 (4)	P = 0.07
Total number of medications per patient at Month 0 (mean/median)	11.07 (11)	11.64 (11)	
Total number of medications per patient at Month 6 (mean/median)	11.5 (11) ($p = 0.094$)	11.09 (11) ($p = 0.0364$)	
Regular medications per patient at Month 0 (mean/median)	5.91 (6)	6.11 (6)	
Regular medications per patient at Month 6 (mean/median)	5.83 (6)	5.55 (5)	

^aData on years in continuing care were obtained on a post hoc analysis of 203 patients. Accurate admission data were not available on the other 22 patients.

G. Pope et al.

Table 2. Number of acute admissions (*n*) in both groups and primary diagnosis on discharge

Study group (n = 11) (11 admissions, 10 Total length of stay 101 days subjects, 1 subject admitted twice) Cholecystitis Pseudo-obstruction of bowel secondary to constipation (not related to medication) Sacral pressure ulcer Abdominal pain secondary to gastritis (not related to suggested medication changes) Gastritis (reduced proton pump inhibitor dose recommended by panel) Fractured femur post-fall Urosepsis ×2 Respiratory tract infection with sepsis ×2 Digoxin toxic and abnormal liver tests (likely medication related) Control group (n = 6)63 days Diverticulitis Fractured femur Cellulitis Severe constipation Stroke Medication-induced GI bleed

specialist input group and occurred despite an increase in the regular input group. The total cost of the study and intervention in the specialist input group (110 patients) was calculated as £56,113 (€59,575). This was the net cost after subtracting the reduction in medication costs. These are service costs excluding study set-up, design and the cost of employing the study nurse.

Quality-of-life measures

A single question regarding whether the intervention had been of benefit was posed to all participating patients with an AMTS ≥ 8 and otherwise to nursing staff familiar with the patient, on their behalf; 95% of the subjects and 98% of the staff felt that this was a positive intervention.

Discussion

The admission of an elderly person to a high-dependency continuing-care setting represents a major point in the overall medical management of frail, dependent persons. It should only take place when modern medicine has reached the limits of its capacity to improve the patient's condition back to a point where they could live independently. Therefore, the treatment of all remediable conditions should already have taken place before such placement. Our randomised study assessed the benefit or otherwise of specialist compared with regular input in patients in continuing care who have been through a thorough evaluation process. This ensures that all opportunities for medical and rehabilitation intervention have been optimised prior to continuing-care admission.

The intervention in this study consisted of a medical assessment by senior doctors trained in geriatric medicine, a specialty already known to have a major impact on acute medical care of the elderly [21, 22]. Medication advice was provided by an expert, multidisciplinary panel to the patient's regular general practitioner. The expert medical advice was drawn from three consultant geriatricians trained in UK academic departments and involved in the UK and Irish Higher Medical Training of specialist registrars. All the geriatricians were registered in the European, UK and Irish Systems of higher specialist accreditation, one with additional North American licensing. The panel also included senior pharmacists with particular expertise in complex elderly prescribing. Implementation of the panel's advice was at the discretion of the general practitioner.

In summary, our large multidisciplinary panel (including geriatrician, pharmacist and nursing representatives) was an attempt to aim for consensus prescribing, thus eliminating any idiosyncratic individual prescribing for the purpose of the research study. As the study was designed to compare specialist geriatric intervention with regular medical officer intervention, we decided that it was inappropriate to include medical officers in the multidisciplinary medication review panel. However, in a future service model, the number of personnel could be significantly reduced and medical officer involvement would be appropriate.

As outlined above, there was a trend towards more nursing requests for clinical evaluation by the general practitioner in the specialist input group, with a higher rate of referral to the acute hospital than in the regular input group. This may have occurred as a result of adverse events due to drug alterations or perhaps it was due to an awareness that these patients were in the intervention group. The increased rate of medical consultation and hospital admission could also have occurred due to a chance baseline imbalance in potentially important prognostic factors such as mean Barthel Index (5.95 versus 6.75 for the specialist versus regular input group, respectively; Table 1). Of further note, the study nurse was blind to randomisation and inputs. However, the ward nurses and the general practitioner were not blind to the intervention and this was a potential source of bias.

In the measurable, hard outcomes such as cost, mortality and functional outcomes, there were no significant differences observed in this study. However, there were lower-level benefits. There was a significant reduction in the total number of medicines prescribed in the specialist input group. This follows a pattern similar to that found as a result of pharmacist medication review in residents of care homes, a less dependent group [18, 23]. The cost saving in our study was outweighed by the significant cost of specialist intervention. One could argue that the cost saving due to a reduction in medications might increase with more frequent implementation over longer periods. There could be additional benefits such as reduced nursing time required for medication administration. The initially disappointing

impact of specialist intervention suggested by our study might then be reviewed.

To our knowledge, this is the first study where specialist geriatric medical input into the management of patients in a continuing-care setting has been evaluated in a randomised, controlled fashion. It is very likely that this group of patients had probably maximised their medical and rehabilitation potential prior to admission to the continuing-care wards, hence being less likely to benefit greatly from further intensive input. However, good prescribing remains essential, and benefits may be reflected in symptomatic well-being rather than in functional measures or mortality (e.g. new medications were recommended by the panel in

Our population is representative of high-dependency patients elsewhere who have undergone a similar thorough multidisciplinary pre-assessment prior to admission to continuing care. We suggest that additional regular structured specialist input provides no mortality benefit at this late stage but can reduce medication cost and may have less tangible symptomatic benefits. These patients with low functional reserve may be managed expectantly with symptomatic treatments instigated by their general practitioners as appropriate. Specialists should be readily available to see patients on request, with geriatric expertise focused on patient selection, optimisation prior to continuing-care admission, maintaining standards of care and input for complex individual cases.

The findings of this study need re-evaluation in other centres. However, our study did involve major numbers in both rural and urban settings as well as an intense medical input. It strongly suggests that for frail elderly, who have been medically optimised and highly screened prior to admission to continuing care, routine input of specialist medical expertise results in a reduction in medication numbers but at a significant cost. The impact of specialist geriatric input may be greater in areas such as early acute medical intervention, rehabilitation, pre-assessment and supervising medical input in continuing care.

Key points

76% of patients).

- Specialist geriatric medication review in continuing-care patients did not improve mortality or frequency of admission to acute hospital care.
- Specialist geriatric medication review in continuing-care patients did not improve hard clinical outcomes but reduced cost.
- Specialist geriatric medication review in continuing-care patients led to a reduction in medication use.

Acknowledgements

We sincerely thank the patients, relatives, nurses and general practitioners of St Ita's and St Camillus' Hospitals for their

Specialist medication review in continuing care

valued assistance with this study. We would like to thank Dr AK Banerjee, Dr John Cooke and Dr Thomas Walsh for their significant contribution to the paper. We deeply appreciate the input from Ms Irene O'Connor in supporting the project.

Conflicts of interest

We declare that we have no conflict of interest.

References

- **1.** Lindley CM, Tully MP, Paramsothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age Ageing 1992; 21: 294–300.
- **2.** Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA (France) 1998; 279: 1200–5.
- **3.** Bates DW, Cullen DJ, Laird N *et al.* Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 1995; 274: 29–34.
- Perri M III, Menon AM, Deshpande AD et al. Adverse outcomes associated with inappropriate drug use in nursing homes. Ann Pharmacother 2005; 39: 405–11.
- Primrose WR. Community institutional care for frail elderly people. 'Unitary care' homes might be the answer. BMJ 1998; 316: 780.
- 6. Hoek JF, Ribbe MW, Hertogh CM, van der Vleuten CP. The role of the specialist physician in nursing homes: the Netherlands' experience. Int J Geriatr Psychiatry 2003; 18: 244_9
- 7. Bootman JL, Harrison DL, Cox E. The health care cost of drug-related morbidity and mortality in nursing facilities. Arch Intern Med (Germany) 1997; 157: 2089–96.
- Hanlon JT, Schmader KE, Koronkowski MJ et al. Adverse drug events in high risk older outpatients. J Am Geriatr Soc 1997; 45: 945–8.
- **9.** Spinewine A, Schmader KE, Barber N *et al.* Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007; 370: 173–84.
- **10.** Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. Drugs Aging 2005; 22: 69–82.
- Carbonin P, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? J Am Geriatr Soc 1991; 39: 1093–9.
- **12.** Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997; 157: 1531–6.
- **13.** Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003; 163: 2716–24.
- **14.** Naugler CT, Brymer C, Stolee P, Arcese ZA. Development and validation of an improving prescribing in the elderly tool. Can J Clin Pharmacol 2000; 7: 103–7.

- **15.** Oborne CA, Hooper R, Swift CG, Jackson SH. Explicit, evidence-based criteria to assess the quality of prescribing to elderly nursing home residents. Age Ageing 2003; 32: 102–8.
- **16.** Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008; 37: 673–9.
- 17. Howard RL, Avery AJ. Pharmacist-led medication reviews can reduce patient morbidity? Age Ageing 2006; 35: 555–6.
- Furniss L, Burns A, Lloyd Craig S et al. Effects of a pharmacist's medication review in nursing homes. Br J Psychiatry 2000; 176: 563–567.
- O'Mahony D, Gallagher PF. Inappropriate prescribing in the older population: need for new criteria. Age Ageing 2008; 37: 138–41.

- Dalkey NC. Delphi, Santa Monica: The RAND Corporation, 1967; P-3704.
- Reuben DB, Borok GM, Wolde-Tsadik G et al. A randomized trial of comprehensive geriatric assessment in the care of hospitalized patients. N Engl J Med 1995; 332: 1345–50.
- 22. Landefeld CS, Palmer RM, Kresevic DM, Fortinsky RH, Kowal J. A randomized trial of care in a hospital medical unit especially designed to improve the functional outcomes of acutely ill older patients. N Engl J Med 1995; 332: 1338–44.
- **23.** Howard RL, Avery AJ. Pharmacist-led medication reviews can reduce patient morbidity? Age Aging 2006; 35: 555–6.

Received 12 July 2009; accepted in revised form 23 June 2010

Age and Ageing 2011; **40:** 312–318 doi: 10.1093/ageing/afr014 Published electronically 17 March 2011 © The Author 2011. Published by Oxford University Press on behalf of the British Geriatrics Society.

All rights reserved. For Permissions, please email: journals.permissions@oup.com

Mortality associated with delirium after hip-surgery: a 2-year follow-up study

Martin G. Kat¹, Jos F. de Jonghe¹, Ralph Vreeswijk², Tjeerd van der Ploeg³, Willem A. van Gool⁴, Piet Eikelenboom^{4,5}, Kees J. Kalisvaart²

Address correspondence to: J. F. M. de Jonghe. Tel: (+31) 725482380; Fax: (+31) 725482197. Email: j.de.jonghe@mca.nl; M. G. Kat. Tel: (+31) 725482380; Fax: (+31) 725482197. Email: psykat@hetnet.nl

Abstract

Background: delirium after hip-surgery is associated with poor outcome. Few studies examined the mortality risk associated with delirium in elderly hip-surgery patients after 1 year or more. Aim of this study was to examine the hazard risk associated with delirium in elderly hip-surgery patients at 2-year follow-up, controlling for baseline risk factors and interaction effects.

Methods: this is a secondary analysis based on data from a controlled clinical trial evaluating efficacy of haloperidol prophylaxis for delirium conducted in a large medical school-affiliated general hospital in Alkmaar, The Netherlands. Randomised and non-randomised patients (n = 603) were followed-up for 2 years. Predefined risk factors and other potential risk factors for delirium were assessed prior to surgery. Primary outcome was time of death during the follow-up period. Cox proportional hazards were estimated and compared across patients who had postoperative delirium during hospitalisation and those who did not.

Results: a total of 90/603 patients (14.9%) died during the study period and 74/603 (12.3%) had postoperative delirium. Incidence of delirium was higher in patients who died (32.2%) compared with those who survived (8.8%). The interaction effect of delirium by illness severity on mortality was significant after adjusting for predefined delirium risk factors and other potential covariates including study intervention (adjusted Hazard risk = 1.05, 95% CI 1.02–1.08). A total of 14/27 delirium patients who were severely ill on admission died during follow-up versus 15/47 delirium patients who were not (RR 1.63 CI 0.93–2.83).

Department of Geriatric Medicine, Medical Center Alkmaar, Alkmaar, The Netherlands

²Department of Geriatric Medicine, Kennemer Gasthuis, Haarlem, The Netherlands

³Pieter van Foreest Institute for Education and Research, Medical Center Alkmaar, Alkmaar, The Netherlands

⁴Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

⁵Department of Psychiatry, Vrije Universiteit Medical Center, Free University of Amsterdam and University of Amsterdam, Amsterdam, The Netherlands