

1 *Review*

2 Multi-Morbidity and Polypharmacy in Older People: Challenges and Opportunities for  
3 Clinical Practice

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19 **Abstract:** Multi-morbidity and polypharmacy are common in older people and pose a challenge for  
20 health and social care systems especially in context of global population ageing. They are complex  
21 and interrelated concepts in the care of older people that require early detection and patient centred  
22 decision making that are underpinned by the principles of multidisciplinary led comprehensive  
23 geriatric assessment (CGA). Personalised care plans need to remain responsive and adaptable to the  
24 needs of a patient, enabling an individual to maintain their independence.

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26 **Keywords:** multi-morbidity; CGA; frailty; polypharmacy; deprescribing

27

## 28 **Introduction**

29 The number of people aged 60 or over globally are set to rise from 841 million to more than 2 billion  
30 between 2013 and 2050; this equates to 21.1% of the world's population (1). The proportion of people  
31 aged 80 years or over is growing even faster. Estimated to be 125 million in 2015 contrasted to 71  
32 million worldwide at the turn of the millennium. This number is projected to increase by 61 per cent  
33 over the next 15 years, reaching nearly 202 million in 2030 (2). In the UK, a male aged 85 could expect  
34 to live to age 90.8 years and a female to 91.8 years (Office of National Statistics 2016, [ONS.gov.uk](https://www.ons.gov.uk)).  
35 These demographic changes are largely due to the advances in public health and modern medicine  
36 that have allowed people to live with one or more long term conditions. Whilst a cause for  
37 celebration, these changes pose significant challenges in the provision of health and social care to  
38 older people (3, 4).

39 Multi-morbidity refers to the presence of two or more simultaneous long-term health conditions that  
40 may not share a causal link for the individual concerned (4). These can span both physical and  
41 psychosocial domains and include conditions such as cardiovascular disease, metabolic diseases  
42 diabetes and osteoporosis, mental health illness, chronic pain, learning disabilities, sensory  
43 deprivation, as well as substance misuse (5, 6). Multi-morbidity increases with age but is not only

44 limited to older people. For example, in a cross sectional study of over 1 million patients in Scotland,  
45 the prevalence of multi-morbidity was 30.4% in those aged 45-64 years increasing to 81.5% in those  
46 >85 years (7). Higher prevalence of multi-morbidity is present in women, those who have a lower  
47 socio-economic status and educational attainment. In addition, there are racial and ethnic differences  
48 that affect prevalence rates (4, 8).

49 Long-term health conditions account for approximately 50% of general practitioner (GP)  
50 appointments, 64% of hospital outpatient appointments and 70% of inpatient hospital admissions (8)  
51 and is therefore responsible for approximately 70% of the United Kingdom, National Health Service  
52 (UK NHS) current healthcare expenditure. People living with multi-morbidity are at greater risk  
53 work absenteeism, mental health problems, unplanned hospital admission, experience higher rates  
54 of polypharmacy and adverse drug events and have a reduced quality of life (9-13). Living with  
55 multi-morbidity is associated with increased rates of mortality. For example, adults aged >60 years  
56 with  $\geq 2$  or  $\geq 3$  health conditions have a 73% and 172% increased risk of dying respectively, compared  
57 to those who are not multi-morbid (14). The proportion of patients living with multi-morbidity is  
58 likely to climb as life expectancy continues to rise (5) and is fast becoming a global health problem  
59 (15-17).

60 The association with poor outcome is likely to be multifactorial. Health conditions have a tendency  
61 to cluster and interact with other related diseases and can worsen the severity of each disease or result  
62 in the development of a further potentially more serious condition (18). For example, the metabolic  
63 syndrome is characterised by central obesity alongside the presence of insulin resistance,  
64 hypertension and raised cholesterol and triglycerides (19). The interaction of these disease  
65 mechanisms leads to a worsening of each individual condition, as well as an increased risk of  
66 cardiovascular events such as stroke or myocardial infarction (20, 21). Another example relevant for  
67 older people is dementia – where individuals have several co-existent long term conditions often  
68 have impairments in function and are at risk of polypharmacy (22). Patients who are multi-morbid  
69 and have functional limitations experience the poorest health outcomes (23).

70 Healthcare infrastructure has not been optimised to manage multiple diseases simultaneously, which  
71 can lead to disorganised care for those who are multi-morbid. The norm amongst most medical  
72 professionals out with geriatric medicine is to specialise and manage single organ systems, or even a  
73 single disease within a given specialty. Whilst this is sometimes necessary, treating diseases in  
74 isolation leads to the duplication of efforts within the healthcare system as well as fragmented, poorly  
75 co-ordinated healthcare assessments and follow up (24-26). The emphasis on managing single  
76 diseases in isolation ignores the unique dynamics of disease clusters. Clinical trials of new  
77 medications often exclude participants who have an additional health problem to the one being  
78 investigated (27-30). This causes uncertainty regarding the potential risks and benefits of starting  
79 evidenced based medications for a patient in the context of their multi-morbidity and invariably leads  
80 to additional treatment burden, lower adherence and increased risk of adverse drug interactions  
81 (ADR) (31).

82

### 83 **Management of multi-morbidity**

84 Key points to managing individuals living with multi-morbidity include early identification of those  
85 living with multiple health conditions, identification of frailty and patient centred shared decision  
86 making (32-34). These key points embody the core principles of comprehensive geriatric assessment

87 (CGA) where a holistic and balanced approach to individualise and prioritise management opinions  
88 take centre stage. Exploring a person's personal goals, which health problems have the most impact  
89 on their day-to-day life and choice on their medication regime allows a tailored approach, which can  
90 facilitate an improvement in individual quality of life. Practical guidance for the management of  
91 multi-morbidity underpinned by core principles of CGA are summarised in **Figure 1**.

92

### 93 **Relationship between multi-morbidity and frailty**

94 Multi-morbidity and frailty are associated conditions, and there may be inevitable overlap between  
95 these concepts in older adults especially since the presence of multiple co-existent conditions  
96 increases the risk of a chronic pro-inflammatory state, hormonal dysregulation and susceptibility to  
97 disease states and hospitalisation (35). Frailty characterised by a vulnerability to stressor events that  
98 can be both internal (e.g. infections and changes to medication) as well as external (e.g. changes in a  
99 person's immediate environment or a breakdown in social care) (36, 37) as a consequence of poor  
100 reserve across multiple physiological systems (38). A recent meta-analysis of 78,122 participants  
101 across 48 studies found that, on average, seven out of ten frail adults were also multi-morbid (39).  
102 However, people living with multi-morbidity will not necessarily also be frail, as many people with  
103 multiple health conditions have the sufficient physiological reserve to recover from insults and return  
104 to their previous baseline of health.

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### 106 **Polypharmacy**

107 Polypharmacy, defined as the concurrent use of at least 4-5 medications rises considerably as the  
108 number of health problems and healthcare service use increases (40, 41). In the health survey for  
109 England 2016, 56% of individuals aged 85 and over were taking five or more medicines compared to  
110 9% of those aged 45-54. A study of 180,815 primary care records found that amongst patients with  
111 two comorbidities, 20.8% received four to nine medications and 1.1% received ten or more  
112 medications (42). In contrast, amongst patients with six or more comorbidities, these values increased  
113 to 47.7% and 41.7% respectively. Several studies have also found that number of medications  
114 increased after hospital admission with prescription on average of two additional drugs (43, 44).

115 In the past decade the average number of items prescribed for each person per year in England has  
116 increased. For example, the proportion of patients receiving  $\geq 10$  medications was 1.9% in 1995,  
117 increasing to 5.8% in 2010 (40). One explanation for this rise is that asymptomatic people are  
118 increasingly treated with preventative interventions to reduce their future risk of mortality; this is  
119 seen particularly with cardiovascular disease. If each morbidity illness is treated in accordance to  
120 national guidelines patients would be on many more medications (45).

121 Polypharmacy is appropriate in instances where medicines have been optimised and prescribed for  
122 complex conditions according to best evidence. Advanced age in itself should not be a reason for  
123 withholding effective therapies (46). Problematic polypharmacy occurs when there is the prescription  
124 of multiple medicines and the risk of harm outweighs benefits and the consequent pill burden leads  
125 to lower adherence or risks of potentially harmful interactions (ADR) (46). ADR can lead to further  
126 morbidity. For example, within two hospitals in the UK, a study suggested that the prevalence of  
127 ADR related admissions was 6.5%, with ADR directly leading to acute admission in 80% of cases (47).  
128 In a follow up study of hospital wards, it was estimated that one in seven patients experienced a ADR  
129 that contributed to health deterioration and increased length of hospital stay (48).

### 130 *Managing polypharmacy*

131 Balancing the recommendations of multiple guidelines for those who are multi-morbid inevitably  
132 leads to polypharmacy and danger of the prescribing cascade where medications are prescribed to  
133 counter side-effects of another medication. Medicines optimisation is defined as a person-centred,  
134 evidence based, approach to safe and effective medicines use to ensure people obtain the best possible  
135 outcomes from their medicines and that they continue to provide benefit for the individual.  
136 Medicines optimisation ensures that there is a specific and justifiable reason for every medication the  
137 patient is taking and that this is as optimum it can be based on evidence. This includes stopping  
138 medications that are having no benefit or causing side effects, interacting and or are contra-indicated  
139 (49). Several guides are available to help with medicines optimisation such as the Beers Criteria,  
140 Medications Appropriateness Index, STOPP-START, NO TEARS and the PINCER tool (50-53). These  
141 guides rely on actions taken by all health and social care practitioners and requires patient  
142 engagement and professional collaboration across health and social care settings (54, 55).  
143 Deprescribing requires an intimate knowledge of drug pharmacodynamics and potential for side  
144 effects and ADR and patient factors affecting pharmacokinetics. When planned, is patient centred  
145 and backed up by education and training, deprescribing is not associated with and significant side  
146 effects or adverse outcomes (56-58).

### 147 *Medication use in older people*

148 Physiological changes with age include a reduction in total body water, increase in blood brain barrier  
149 permeability, lower hepatic mass, decreased renal cortical mass, lower nephron numbers and a lower  
150 capacity for glomerular filtration. Older people have mild renal impairment and this is not always  
151 reflected by a rise in serum creatinine due to sarcopenia. These changes increase the risk of ADR and  
152 potentially harmful drug-drug interactions. This especially important for drugs with a narrow  
153 therapeutic index (NTI) such as digoxin, warfarin, aminophylline, lithium and some antidepressants.  
154 In addition, older people are more susceptible to anticholinergic side effects from commonly  
155 prescribed drugs such as amitriptyline, oxybutynin, cetirizine, mirtazapine, which include delirium,  
156 reduced cognition, gait and balance problems, constipation, urinary retention and dry mouth (59).  
157 These conditions may be misinterpreted as new conditions and can initiate a prescribing cascade.  
158 Individuals who have a shorter life expectancy may not benefit from prescribed medications that take  
159 time before therapeutic benefit is established. Examples include anti-hypertensives, drugs used to  
160 treat hyperlipidaemia and osteoporosis treatments (60). Given the heterogeneity of disease  
161 trajectories in older people, symptoms and individual patient preferences, goals of care will vary  
162 between individuals. This should be driven by patient centred decision making, underpinned by  
163 CGA (61).

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### 167 **Comprehensive geriatric medicine (CGA): a useful paradigm in the management of older people** 168 **across primary and secondary care.**

169 Individuals generally do not like taking prescribed medications for several reasons such as complex  
170 dosing regimens, fear, scepticism especially when asymptomatic, and media portrayal. These factors  
171 affect adherence and studies suggest that up to 50% of prescribed medications may not be taken by  
172 older people (62). GPs are in a position to make shared decisions with patients and families to

173 prescribe, deprescribe, rationalise and optimise medications (54, 63). It is also clear that the impact of  
174 multi-morbidity, frailty and polypharmacy spans both primary and secondary care. Geriatricians and  
175 pharmacists are therefore also ideally placed within the MDT and alongside GPs to implement  
176 principles of personalised care planning consequent to CGA across this arbitrary divide. This  
177 provides an exciting opportunity for future models of care (64) (**Figure 1**).

178

### 179 **Conclusions**

180 Older age is characterised by and increased risk of accumulating multiple long term conditions.  
181 Multi-morbidity and polypharmacy are interrelated and are associated with progressive loss of  
182 resilience, impaired homeostasis and contribute to a significant health and social care burden.  
183 Routine assessment of long term conditions, presence of frailty and medicines optimisation should  
184 form part of a patient centred, multidisciplinary, personalised and comprehensive assessment across  
185 all health and social care settings.

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### 188 **Competing interests**

189 The authors declare no conflict of interest

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191 All authors were involved in the preparation of this manuscript. HPP edited and critically revised  
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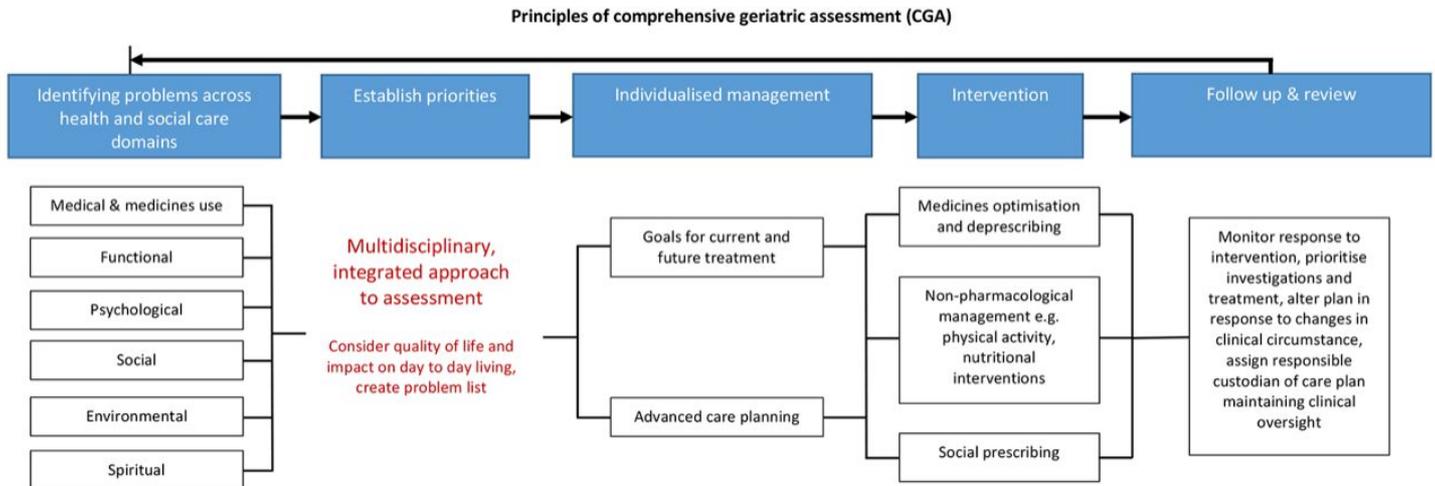
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### 377 **Figure 1 Principles of comprehensive geriatric assessment (CGA)**

378 CGA is an evidence based multidimensional and interdisciplinary assessment of medical,  
 379 psychological and functional capabilities aimed at developing an integrated plan for treatment and  
 380 care and is associated with favourable clinical and health care outcomes. The core principles of CGA  
 381 include comprehensive history taking, multidisciplinary led assessment culminating in goals for  
 382 current and future management. These principles can be applied across any health and social care  
 383 setting and has been shown to be highly effective in the management of older people living with  
 384 frailty and multi-morbidity. The process is iterative and the key to its success is timely review and  
 385 coordination so that the care plan generated from a CGA remains responsive to the patient's needs.

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