International Psychogeriatrics: page 1 of 14
doi:10.1017/S1041610216001307

Patterns of psychotropic prescribing and polypharmacy in older hospitalized patients in Ireland: the influence of dementia on prescribing

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ABSTRACT

Background: Neuropsychiatric Symptoms (NPS) are ubiquitous in dementia and are often treated pharmacologically. The objectives of this study were to describe the use of psychotropic, anti-cholinergic, and deliriogenic medications and to identify the prevalence of polypharmacy and psychotropic polypharmacy, among older hospitalized patients in Ireland, with and without dementia.

Methods: All older patients (≥ 70 years old) that had elective or emergency admissions to six Irish study hospitals were eligible for inclusion in a longitudinal observational study. Of 676 eligible patients, 598 patients were recruited and diagnosed as having dementia, or not, by medical experts. These 598 patients were assessed for delirium, medication use, co-morbidity, functional ability, and nutritional status. We conducted a retrospective cross-sectional analysis of medication data on admission for 583/598 patients with complete medication data, and controlled for age, sex, and co-morbidity.

Results: Of 149 patients diagnosed with dementia, only 53 had a previous diagnosis. At hospital admission, 458/583 patients experienced polypharmacy (≥ 5 medications). People with dementia (PwD) were significantly more likely to be prescribed at least one psychotropic medication than patients without dementia (99/147 vs. 182/436; $p < 0.001$). PwD were also more likely to experience psychotropic polypharmacy (≥ two psychotropics) than those without dementia (54/147 vs. 61/436; $p < 0.001$). There were no significant differences in the prescribing patterns of anti-cholinergics (23/147 vs. 42/436; $p = 0.18$) or deliriogenics (79/147 vs. 235/436; $p = 0.62$).

Conclusions: Polypharmacy and psychotropic drug use is highly prevalent in older Irish hospitalized patients, especially in PwD. Hospital admission presents an ideal time for medication reviews in PwD.

Key words: dementia, delirium, anti-psychotics, behavioral and psychological symptoms of dementia (BPSD), neuropsychiatric symptoms (NPS)

Introduction

The number of people with dementia (PwD) is escalating worldwide; estimates project the prevalence at over 131.5 million by 2050 (Alzheimer's Disease International, 2015). The majority will experience Behavioral and Psychological Symptoms of Dementia (BPSD), also referred to as Neuropsychiatric Symptoms (NPS) during their disease (Lawlor, 2002). BPSD refers to the spectrum of distressing, non-cognitive symptoms of dementia, ranging from wandering and agitation to delusional and aggressive behavior (Cahill *et al.*, 2012). Psychotropic medications are commonly prescribed to manage BPSD and have some evidence to support their use (Bishara *et al.*, 2009; Seitz *et al.*, 2013). For example, the CitAD trial showed that the addition of citalopram to a psychosocial intervention was more effective at reducing agitation and caregiver distress in PwD than the addition of placebo (Porsteinsson

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et al., 2014). Furthermore, treatment of BPSD with atypical anti-psychotics has been found to cause a small yet significant reduction in caregiver burden (Mohamed *et al.*, 2012). However, anti-psychotics are known to increase the risk of stroke and mortality in PwD (Schneider *et al.*, 2005), and a recent study has found that for every 26 PwD treated with haloperidol, there was one death (Maust *et al.*, 2015). Additionally, the DIADS-2 trial found that sertraline was not efficacious for the treatment of depression in PwD and was associated with an increased risk of adverse events (Rosenberg *et al.*, 2010; Weintraub *et al.*, 2010). Guidelines generally recommend that non-pharmacological treatments should be used as first-line treatment of BPSD, and only when these fail should psychotropic agents be trialed for short-term use (Azermai *et al.*, 2012). Despite this, the usage of anti-psychotics and other psychotropics in this vulnerable patient group remains unacceptably high (Maust *et al.*, 2016).

Polypharmacy, which is defined as the use of five or more medications (Gnjidic *et al.*, 2012), is common in older people and is associated with poorer health outcomes (Hajjar *et al.*, 2007). Similarly, psychotropic polypharmacy (concurrent use of two or more psychotropic agents) increases the risk of adverse events (Mojtabai and Olfson, 2010). Delirium super-imposed on dementia is often drug-related and medications such as opioids and benzodiazepines can trigger a delirium episode in susceptible people (Clegg and Young, 2011). Also, anti-cholinergic medications can negatively affect cognitive and physical function in older people and their use should be minimized in PwD (Collamati *et al.*, 2016).

Hospitalization in PwD is associated with significantly poorer health outcomes (Zekry *et al.*, 2009). PwD are particularly vulnerable in this setting, due to the challenges of illness, new medications, and unfamiliar environments/carers (Borbasi *et al.*, 2006). The report of the Irish National Audit of Dementia (INAD) care in acute hospitals found high levels of anti-psychotic prescribing in hospitalized PwD, particularly when admitted from nursing homes (de Siún *et al.*, 2014). The authors highlighted a need for regular medication review on admission, echoed in the recently published Irish National Dementia Strategy (Department of Health, 2014). However, only 20 healthcare records from each hospital were reviewed for anti-psychotic prescribing in this audit (de Siún *et al.*, 2014). Furthermore, only people with an explicit diagnosis of dementia who had a minimum length of stay of five days were included. Therefore, it is unclear whether this data is representative of the majority of Irish PwD who are admitted to hospital.

The objectives of this study were to describe the use of psychotropic, anti-cholinergic, and deliriogenic medication among older hospitalized patients, with and without dementia, and to identify the prevalence of polypharmacy (≥5 medications) and psychotropic polypharmacy (concurrent use of ≥2 psychotropic agents) in these patient groups. Our research question was "Are there any differences in the patterns of prescribing between older people (≥70 years) with and without dementia, upon admission to six acute hospitals in the south of Ireland, controlling for age, sex and co-morbidity?" Our primary hypothesis was that PwD are significantly more likely to be prescribed psychotropics and to be exposed to psychotropic polypharmacy than people without dementia, as previously reported (Giron *et al.*, 2001; Hartikainen *et al.*, 2003). Our secondary hypothesis was that PwD are more likely to be prescribed deliriogenic and anti-cholinergic medications and to be prescribed more medications than people without dementia; however, the evidence for this is mixed or lacking (Schmader *et al.*, 1998; Andersen *et al.*, 2011).

Methods

Study design, setting, and patients

The Cork Dementia Study has been described in detail elsewhere (Timmons *et al.*, 2015). In brief, this longitudinal observational study explored the prevalence and associations of dementia in older patients admitted to all six acute hospitals in County Cork, Ireland. County Cork has a population of 519,032 which is comprised of 49.61% males, an older population (≥70 years) of 42,382 (Central Statistics Office, 2012) and an estimated dementia population of 4,830 (Cahill *et al.*, 2012). This is relatively comparable to the proportions for the Republic of Ireland as a whole (total population = 4,588,252; males = 49.53%; older population ≥70 years = 361,755; and estimated dementia population = 41,720).

Eligibility criteria for this study included age ≥70 years old and elective or emergency admission (non-day case). Recruitment occurred in each hospital for a period of two weeks and lasted from May 2012 to February 2013. Informed consent was obtained for all patients. Exclusion criteria included patient refusal or being moribund on arrival to hospital. Patients were diagnosed with dementia by a three-step approach, involving initial cognitive screening utilizing the Standardized Mini-Mental State Examination, followed by informant-derived data utilizing the Informant Questionnaire on Cognitive Decline in the Elderly. Finally,

dementia status was established by the senior author (ST), a consultant geriatrician, based on all available information (i.e. cognitive testing, informant-derived data, medical and demographic history). Patients were also assessed for delirium, depression, medication use, co-morbidity, functional ability, and nutritional status. Data were prospectively collected by researchers with nursing or psychology backgrounds, after extensive training in all assessment tools.

This present study is a retrospective cross-sectional analysis of the original Cork Dementia Study medication data, collected on admission. First, the original medication data were cleaned by the study pharmacist (KAW), using a three-step cycle of screening, diagnosing, and editing suspected data irregularities, for the purpose of ensuring that incorrectly spelled or partially filled entries could be corrected and coded accurately (Van den Broeck *et al.*, 2005). Second, the cleaned medication data were coded by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classifications (WHO, 2015), excluding emollients or nutritional supplements without any active ingredients. Information on strength, quantity, duration, or usage at follow-up, were not recorded consistently so were not coded. Patients with missing medication data were excluded from the analysis. Finally, the coded medication data were cleaned again and linked at individual patient-level to the previously coded clinical data.

The "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines have been followed in the conduct and reporting of this research (Von Elm *et al.*, 2007). Ethical approval was obtained from the local ethics committee (reference ECM 4 (t) 06/12/11 & ECM 3 (yy) 07/07/15).

Prescribing patterns

The primary outcome in this study was the difference in prescribing patterns between people with and without dementia, particularly psychotropic agents in PwD, and especially anti-psychotics. The definition of a psychotropic varies significantly throughout the literature; the research group, by consensus, included anti-psychotics (N05A), anti-depressants (N06A), anxiolytics (N05B), hypnotics (N05C), anti-convulsants/mood-stabilizers (N03A), and anti-dementia drugs (N06D), as these medication classes are used to manage BPSD (Bishara *et al.*, 2009). It is important to acknowledge that anti-dementia drugs are inevitably utilized more in PwD than people without dementia, due to their cognitive enhancing properties. Additionally, some studies do not consider anti-convulsants/mood-stabilizers to be psychotropics (Avorn *et al.*, 1992; Patterson *et al.*, 2010). Therefore, we conducted sensitivity analyses to assess the impact of more conservative psychotropic definitions on our outcomes by excluding the following in a step-wise manner:

1. N06D (Anti-dementia drugs),
2. N06D and N03A (Anti-dementia drugs and anti-convulsants/mood-stabilizers).

We utilized ATC codes, but reclassified Lithium (N05AN01) as a mood-stabilizer rather than an anti-psychotic (Søndergård *et al.*, 2008). We were also interested in psychotropic polypharmacy, and patterns of anti-psychotic prescribing in those admitted from nursing homes. Other prescribing patterns of interest included the 14 main ATC anatomical groups (excluding "D- Dermatologicals"), levels of minor or major polypharmacy (5–9 medications; or $\geq$10 medications, respectively), deliriogenic medications and anti-cholinergics. Deliriogenic medication definition was based on published literature, decided upon by consensus between the study pharmacist (KAW) and two consultant geriatricians (ST, NOR) who are delirium experts. The included deliriogenic medications were predominantly in line with findings from a systematic review conducted by Clegg *et al.* which investigated the associations between medications and risk of delirium (Clegg and Young, 2011). These definitions and the associated ATC codes are shown in Table 1.

Statistical analysis

The original data were entered into a FileMaker Pro 11 database and subsequently exported into Excel 2011 for ATC coding and linking, before transferal into STATA software version 13 (StataCorp, College Station, TX, USA) for data analysis; statistical significance at p-value < 0.05 was assumed. Descriptive statistics were utilized to summarize the population. Differences in prescribing patterns between those with and without dementia were assessed using the χ^2 test (Fisher's exact test if expected cell frequency was <5) for categorical variables, and Student's t-test (normally distributed) or Mann–Whitney U test (non-normally distributed) for continuous variables. To control for age, sex, and co-morbidity (Cumulative Illness Rating Scale in Geriatrics) effects, these were entered as independent variables into a model for each dependent variable, utilizing multivariate linear, or logistic regression, for continuous or binary dependent variables, respectively. Results are reported in terms of adjusted odds

Table 1. Drug class definitions by WHO-ATC code

DRUG CLASS	WHO ATC CODE
Psychotropic	
Anti-psychotic	N05A (except N05AN01 – Lithium)
Anti-depressant	N06A
Anxiolytic	N05B
Hypnotics	N05C
Anti-convulsants/mood stabilizers	N03A (including N05AN01 – Lithium)
Anti-dementia drugs	N06D
Potentially Deliriogenic Drugs as decided *a priori* by consensus	
Benzodiazepines	N05BA, N05CD, N03AE01
Opioids	N02A, N01AH, N02BE51, R05DA, R05FA
Dihydropyridines	C08CA
Tricyclic anti-depressants	N06AA
Anti-cholinergics (excluding inhaled/topical)	A03AA, A03AB, A03B, A03CA, A03CB, A03DA, A03DB, A03E, A04AD01 G04BD01-G04BD11, N02AG, N04A, N06AA,
Steroids (excluding inhaled/topical)	H02, A14A, G01B
H_2-receptor antagonists	A02BA
Anti-Parkinson's Drugs	N04
Benzodiazepine-related drugs	N05CF
Other drugs which may increase the risk of delirium but were not included in our *a priori* deliriogenic group	
Anti-psychotics	N05A (except N05AN01 - Lithium)
Non-steroidal anti-inflammatory drugs (NSAIDS)	M01A
Anti-depressants	N06A
Anti-dementia drug	N06D
Anti-convulsant/mood stabilizer	N03A (including N05AN01 - Lithium)
Typical versus atypical anti-psychotics	
Typical anti-psychotics	N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG (except N05AE04 - Ziprasidone)
Atypical anti-psychotics	N05AH, N05AL, N05AX (including N05AE04 - Ziprasidone)

WHO ATC = world health organization anatomical therapeutic chemical.

ratios (aOR) and their 95% confidence intervals (95% CI).

Results

Study population characteristics

Of 676 patients eligible for study enrolment, 598 were recruited and had a diagnosis of dementia or no dementia assigned (Figure 1). In total, a quarter of patients had dementia ($N = 149$); 53/149 (35.5%) had a known diagnosis prior to the study, and another 16/149 (11%) had known cognitive impairment. Eighty patients (53.5%) were diagnosed with dementia *de-novo* in the study, 29% ($N = 23$) of whom had moderate or severe dementia.

Fifteen patients had missing medication data, resulting in 583 patients (86% of all admissions) with linked medication and clinical data. There was no significant difference in terms of the proportion of patients with missing medication data between those with and without dementia ($\chi^2 = 1.1$; p-value $= 0.29$). Just under half of the study population were male (49%; $N = 285$), the median age was 79 years (Interquartile range = 74–84) and the vast majority were admitted from a home environment (own home, children's home, or social/sheltered accommodation) (91%; $N = 530$) (Table 2). PwD were significantly older, more dependent, and had higher co-morbidities than those without dementia (all p-values < 0.001). PwD were also significantly more likely to be admitted from a nursing home, to be acutely admitted to hospital, or to have delirium on admission (all p-values ≤ 0.001). One-fifth ($N = 115$) of all patients were diagnosed with delirium at admission and PwD constituted the majority of these cases (73%; $N = 84$).

Prescribing patterns

Six patients were taking no medication on admission. PwD were prescribed almost one medication more per patient, on average, than those without dementia (mean ± standard

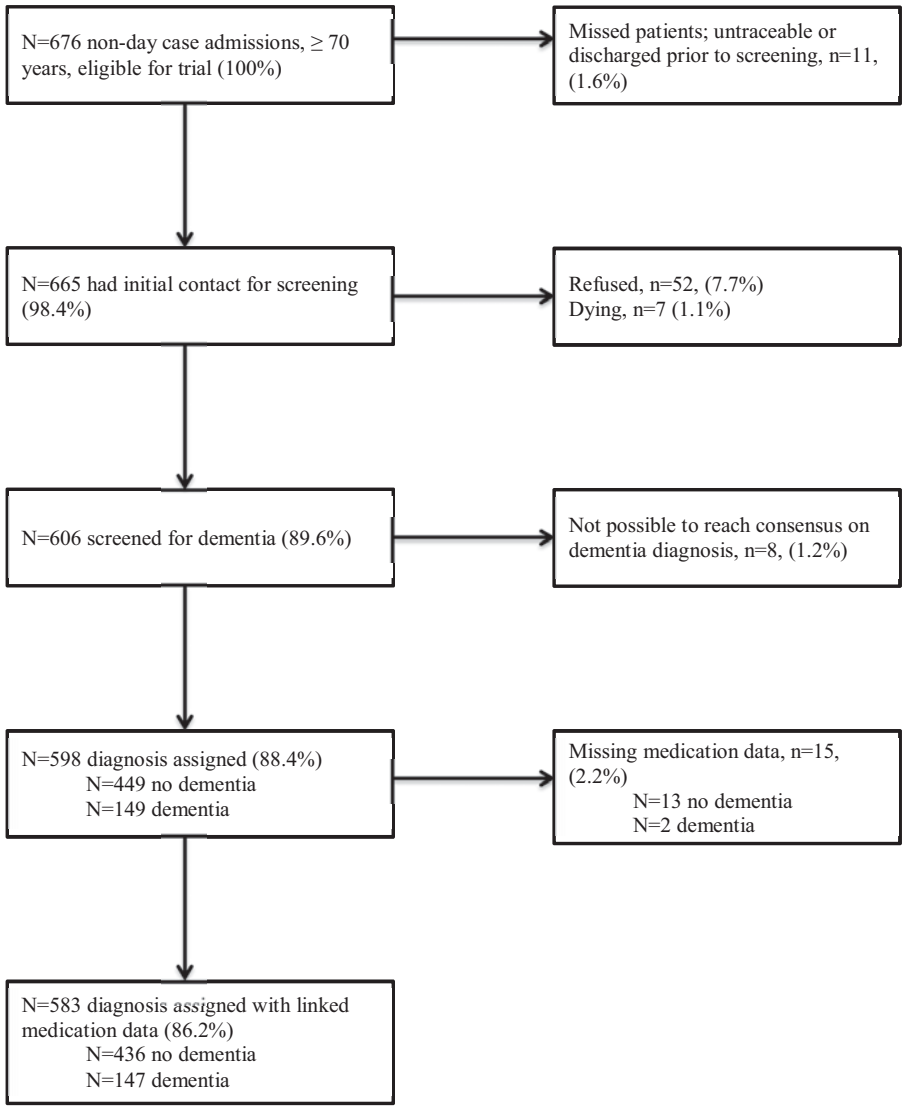

Figure 1. Flow diagram of participant.

deviation = 7.9 ± 3.3 vs. 7.1 ± 3.6; T= −2.1; p-value = 0.04) as shown in Table 3. However, when corrected for age, sex, and co-morbidity, this difference became non-significant (β = 0.3; 95% CI = −0.4–1.0; p-value = 0.43). The prevalence of polypharmacy was 84% in PwD and 77% in people without dementia; however, this difference was not significant (p = 0.08). Furthermore, there was no significant difference between the two groups in terms of the prevalence of major polypharmacy (27% in PwD and 23% in people without dementia; p-value = 0.35).

PwD were significantly more likely to be prescribed at least one psychotropic medication (χ^2 = 28.9; aOR = 2.6, 95% CI = 1.7–4.0; p-value < 0.001). Atypical anti-psychotics, anti-depressants, anxiolytics, and anti-dementia drugs were all significantly more likely to be prescribed to PwD, even controlling for age, sex, and co-morbidity (all p-values < 0.05). However, there was no significant difference in hypnotic, anti-convulsant/mood-stabilizer, or typical anti-psychotic prescription between the two groups (all p-values > 0.05). The prevalence of psychotropic polypharmacy was 37% in PwD and 14% in people without dementia and thus PwD were over three times more likely to experience psychotropic polypharmacy (χ^2 = 35.9; aOR = 3.5; 95% CI = 2.1–5.6; p-value < 0.001). Sensitivity analyses found that even when we excluded anti-dementia drugs and subsequently anti-convulsants/mood-stabilizers from our definition of psychotropics, PwD were still significantly more likely to be prescribed at least one psychotropic (p-values ≤ 0.002) and to be exposed to psychotropic polypharmacy (p-values < 0.001) than those without

Table 2. Demographics of study population

	DEMENTIA ($N = 147$)[a]	NO DEMENTIA ($N = 436$)[b]	TOTAL ($N = 583$)	p - VALUE	MWU/χ^2
Sex, *N* (%)					
Male	63 (42.3)	222 (50.9)	285 (48.9)	0.091	$\chi^2 = 2.9$
Age					
Median	84	78	79	< 0.001*	MWU = −8.2
IQR	79–89	74–82	74–84		
Home type admitted from, *N* (%)					
Home	113 (76.9)	417 (95.6)	530 (90.9)	< 0.001**	$\chi^2 = 56.1$
Nursing home	27 (18.4)	8 (1.8)	35 (6.0)		
Sheltered accommodation	7 (4.8)	11 (2.5)	18 (3.1)		
CIRS-G score					
Median	11	9	10	< 0.001*	MWU = −4.1
IQR	8–15	7–12	7–13		
Barthel index					
Median	11	20	19	< 0.001*	MWU = 12.7
IQR	6–17	17–20	14–20		
Admission type, *N* (%)					
Acute	120 (81.6)	300 (68.8)	420 (72.0)	0.003**	$\chi^2 = 9.0$
Elective	27 (18.4)	136 (31.2)	163 (28.0)		
Delirium on admission, *N* (%)	84 (57.1)	31 (7.1)	115 (19.8)	<0.001**	$\chi^2 = 173.4$

[a]N = two dementia patients without completed medication data.
[b]N = 13 non-dementia patients without completed medication data.
*Statistically significant at p-level < 0.05, utilizing MWU test.
**Statistically significant at p-level < 0.05, utilizing χ^2 test.
MWU = Mann–Whitney U test, CIRS-G = cumulative illness rating scale in geriatrics, IQR = inter-quartile range.

dementia (Table 3). Removing these two classes of medications reduced the prevalence of psychotropic polypharmacy in patients with and without dementia to 29% versus 14% (excluding N06D), and then to 24% versus 10% (excluding N06D and N03A) respectively.

Looking at psychotropic medications in more detail, 32% of PwD were prescribed anti-depressants, compared to 19% of people without dementia ($\chi^2 = 10.1$; aOR = 2.1; 95% CI = 1.3–3.3; p-value = 0.002). Similarly, 14% of PwD ($N = 20$) were prescribed at least one anti-psychotic, compared to 5% of their peers ($N = 21$) ($\chi^2 = 13.0$; aOR = 3.7; 95% CI = 1.8–7.6; p-value < 0.001). In terms of those who had a previous diagnosis of dementia ($N = 53$), 28% ($N = 15$) were prescribed an anti-psychotic, compared to just 5% ($N = 5$) of those who had no prior diagnosis or a diagnosis of cognitive impairment ($N = 94$). Patients admitted from nursing homes were almost five times more likely to be prescribed an anti-psychotic than those who were admitted from home controlling for dementia diagnosis, age, sex, and co-morbidity ($\chi^2 = 26.7$; aOR = 4.8; 95% CI = 1.9–12.1; p-value = 0.001). Atypical anti-psychotics ($N = 30$) were more commonly prescribed than typical anti-psychotics ($N = 14$), predominantly quetiapine ($N = 17$), and olanzapine ($N = 11$).

Just over half of all patients were prescribed ≥1 potentially deliriogenic medication (54%), with no differences in the level of prescribing of these agents between the two groups ($\chi^2 < 0.01$; aOR = 0.9; 95% CI = 0.6–1.4; p-value = 0.6). Benzodiazepines and systemic anti-cholinergics were significantly more likely to be prescribed to PwD (both p-value < 0.05), but differences became non-significant after adjusting for age, sex, and co-morbidity (both p-value > 0.05).

The four most commonly prescribed WHO ATC anatomical groups were (i) cardiovascular system, (ii) blood and blood forming organs, (iii) alimentary tract and metabolism, and (iv) nervous system, prescribed to 87%, 70%, 70%, and 60% of all patients, respectively (see Table S1 published as supplementary material online attached to the electronic version of this paper at www.journals.cambridge.org/jid_IPG). There were no differences in the level of prescribing of any of the 13 included WHO-ATC anatomical groups (all p-values > 0.05), except for nervous system drugs, which were more commonly prescribed to PwD ($\chi^2 = 19.6$; aOR = 2.0, 95% CI = 1.3–3.2; p-value = 0.003).

Table 3. Prescribing patterns in hospitalized patients with and without dementia

	DEMENTIA ($N = 147$)	NO DEMENTIA ($N = 436$)	TOTAL ($N = 583$)	p - VALUE[e]	T-VALUE, χ^2 OR FISHERS EXACT TEST	CONTROLLING FOR AGE, SEX, AND CO-MORBIDITY[f]
Total number of medications prescribed	1154	3117	4271	–	–	–
Number of patients prescribed ≥ 1 medication, *N* (%)	147 (100)	430 (98.6)	577 (99.0)	0.15	$\chi^2 = 1.1$	aOR = 0.9, 95% CI = 0.1–4.7
Number of medications per patient						
Mean	7.9	7.1	7.3	0.04*	$T = -2.1$	$\beta = 0.3$, 95% CI = −0.4–1.0
SD	3.3	3.6	3.5			
Range	1–17	0–20	0–20			
Number of patients who experienced the following levels of polypharmacy, *N* (%):						
Minor polypharmacy (5–9 medications)	83 (56.5)	233 (53.4)	316 (54.2)	0.53	$\chi^2 = 0.4$	aOR = 1.0, 95% CI = 0.7–1.6
Major polypharmacy (≥ 10 medications)	40 (27.2)	102 (23.4)	142 (24.4)	0.35	$\chi^2 = 0.9$	aOR = 1.0, 95% CI = 0.6–1.6
Any polypharmacy (≥ 5 medications)	123 (83.7)	335 (76.8)	458 (78.6)	0.08	$\chi^2 = 3.1$	aOR = 1.1, 95% CI = 0.6–1.9
Number of patients prescribed ≥ 1 of the following psychotropic medications, *N* (%)						
Anti-psychotics	20 (13.6)	21 (4.8)	41 (7.0)	<0.001**	$\chi^2 = 13.0$	aOR = 3.7, 95% CI = 1.8–7.6‡
Typical anti-psychotics	5 (3.4)	9 (2.1)	14 (2.4)	0.36	$\chi^2 = 0.8$	aOR = 1.6, 95% CI = 0.5–5.5
Atypical anti-psychotics	16 (10.9)	13 (3.0)	29 (5.0)	<0.001**	$\chi^2 = 14.5$	aOR = 4.7, 95% CI = 2.0–10.9‡
Anti-depressants	47 (32.0)	84 (19.3)	131 (22.5)	0.001**	$\chi^2 = 10.1$	aOR = 2.1, 95% CI = 1.3–3.3‡
Anxiolytics	21 (14.3)	27 (6.2)	48 (8.2)	0.002**	$\chi^2 = 9.5$	aOR = 2.3, 95% CI = 1.2–4.6‡
Hypnotics	29 (19.7)	74 (17.0)	103 (17.7)	0.45	$\chi^2 = 0.6$	aOR = 0.9, 95% CI = 0.5–1.5
Anti-convulsants/mood-stabilizer	16 (10.9)	50 (11.5)	66 (11.4)	0.85	$\chi^2 = 0.03$	aOR = 0.9, 95% CI = 0.5–1.7
Anti-dementia drugs	35 (23.8)	3 (0.7)	38 (6.5)	<0.001**	$F < 0.001$	aOR = 47.9, 95% CI = 13.8–166.3‡
Any psychotropic medication[a]	99 (67.4)	182 (41.7)	281 (48.2)	<0.001**	$\chi^2 = 28.9$	aOR = 2.6, 95% CI = 1.7–4.0‡
Any psychotropic medication *(excluding anti-dementia dugs)*	83 (56.5)	182 (41.7)	265 (45.5)	0.002**	$\chi^2 = 9.6$	aOR = 1.6, 95% CI = 1.1–2.4‡

Table 3. Continued.

	DEMENTIA (N = 147)	NO DEMENTIA (N= 436)	TOTAL (N= 583)	p - VALUE[e]	T-VALUE, χ^2 OR FISHERS EXACT TEST	CONTROLLING FOR AGE, SEX, AND CO-MORBIDITY[f]
Any psychotropic medication *(excluding anti-dementia drugs and anti-convulsants/mood-stabilizers)*	75 (51.0)	155 (35.6)	230 (39.5)	0.001**	$\chi^2 = 11.0$	aOR = 1.7, 95% CI = 1.1–2.5‡
Number of patients who experienced the following levels of psychotropic prescribing, *N* (%)						
No psychotropic medication prescribed[a]	48 (32.7)	254 (58.3)	302 (51.8)	<0.001**	$\chi^2 = 28.9$	aOR = 0.4, 95% CI = 0.2–0.6‡
Only one psychotropic medication prescribed[a]	45 (30.6)	121 (27.8)	166 (28.5)	0.5	$\chi^2 = 0.4$	aOR = 1.0, 95% CI = 0.6–1.6
Psychotropic Polypharmacy[a] (≥ 2 psychotropics)	54 (36.7)	61 (14.0)	115 (19.7)	<0.001**	$\chi^2 = 35.9$	aOR = 3.5, 95% CI = 2.1–5.6‡
Psychotropic Polypharmacy (≥ 2 psychotropics) *(excluding anti-dementia dugs)*	43 (29.3)	60 (13.8)	103 (17.7)	<0.001**	$\chi^2 = 18.1$	aOR = 2.5, 95% CI = 1.5–4.1‡
Psychotropic polypharmacy (≥ 2 psychotropics) *(excluding anti-dementia dugs and anti-convulsants/mood stabilizers)*	35 (23.8)	44 (10.1)	79 (13.6)	<0.001**	$\chi^2 = 17.7$	aOR = 2.7, 95% CI = 1.5–4.6‡
Number of patients prescribed ≥ 1 of the following potentially deliriogenic medication[b], *N* (%)						
Benzodiazepines	32 (21.8)	52 (11.3)	84 (14.4)	0.003**	$\chi^2 = 8.6$	aOR = 1.7, 95% CI = 0.9–2.9
Opioids	18 (12.2)	78 (17.9)	96 (16.5)	0.11	$\chi^2 = 2.5$	aOR = 0.7, 95% CI = 0.4–1.3
Dihydropyridines	18 (12.2)	72 (16.5)	90 (15.4)	0.22	$\chi^2 = 1.5$	aOR = 0.8, 95% CI = 0.4–1.4
Tricyclic anti-depressants	9 (6.1)	17 (3.9)	26 (4.5)	0.26	$\chi^2 = 1.3$	aOR = 1.5, 95% CI = 0.6–3.6

Table 3. Continued.

	DEMENTIA ($N = 147$)	NO DEMENTIA ($N = 436$)	TOTAL ($N = 583$)	p - VALUE[e]	T-VALUE, χ^2 OR FISHERS EXACT TEST	CONTROLLING FOR AGE, SEX, AND CO-MORBIDITY[f]
Systemic anti-cholinergics[c]	23 (15.7)	42 (9.6)	65 (11.2)	0.045**	$\chi^2 = 4.0$	aOR = 1.5, 95% CI = 0.8–2.8
Systemic steroids	7 (4.8)	40 (9.2)	47 (8.1)	0.09	$\chi^2 = 2.9$	aOR = 0.4, 95% CI = 0.1–0.9^
H_2-receptor antagonists	2 (1.4)	2 (0.5)	4 (0.7)	0.27	$F = 0.27$	aOR = 2.5, 95% CI = 0.3–23.4
Anti-Parkinson's drugs	6 (4.1)	9 (2.1)	15 (2.6)	0.18	$\chi^2 = 1.8$	aOR = 2.0, 95% CI = 0.6–6.4
Benzodiazepine-related drugs	14 (9.5)	46 (10.6)	60 (10.3)	0.72	$\chi^2 = 0.1$	aOR = 0.7, 95% CI = 0.4–1.4
Any potentially deliriogenic drug	79 (53.7)	235 (53.9)	314 (53.9)	0.97	$\chi^2 < 0.01$	aOR = 0.9, 95% CI = 0.6–1.4
Systemic NSAID[d]	5 (3.4)	29 (6.7)	34 (5.8)	0.15	$\chi^2 = 2.1$	aOR = 0.5, 95% CI = 0.2–1.5

[a]Psychotropic defined as anti-psychotics, anti-depressants, anxiolytic, hypnotics, anti-convulsants/mood-stabilizer, and anti-dementia drugs.
[b]Deliriogenic medications defined by group consensus *a priori*.
[c]Systemic anti-cholinergics defined by group consensus *a priori*.
[d]Systemic non-steroidal anti-inflammatory drugs not included in the potentially deliriogenic drug category, but shown here for illustration purposes.
[e]p-value for two-way table with measures of association.
[f]Adjusted odds ratio for dependent variable utilizing linear or logistic regression as appropriate, with age, sex, and CIRS-G as the independent variables.
*Statistically significant at p-level < 0.05, utilizing Student's t-test.
**Statistically significant at p-level < 0.05, utilizing χ^2 test or Fishers exact test.
‡Statistically significant at p-level < 0.05, utilizing logistic regression.
^Although significant at p-level < 0.05, this variable does not contain a minimum of ten cases of event and no event that are usually required for logistic regression analysis, therefore the findings should not be interpreted as statistically significant.
CIRS-G = Cumulative Illness Rating Scale in Geriatrics, aOR = adjusted odds ratio, NSAID = Non-steroid anti-inflammatory drug, β = beta- coefficient, 95% CI = 95% confidence interval.

Discussion

Main findings

This retrospective cross-sectional study aimed to explore the prescribing patterns of psychotropic, anti-cholinergic, and deliriogenic medications, and polypharmacy, in a well-defined cohort of hospitalized older Irish patients; and to assess whether having dementia influenced these prescribing patterns. Overall, we found that this population was prescribed high levels of medication, with over two-thirds experiencing polypharmacy and a quarter experiencing major polypharmacy. PwD were more likely to be prescribed psychotropic medications and to experience psychotropic polypharmacy. We found no differences in the prescribing patterns in terms of number of medications, anti-cholinergic medications, deliriogenic medications, or any of the other main WHO ATC anatomical groups, except for nervous system medications.

Another important finding of the Cork Dementia Study was that only 35.5% of PwD had an explicit diagnosis of dementia prior to the study. Previous studies conducted in Australia (Travers *et al.*, 2013) and the UK (Sampson *et al.*, 2009) reported similar levels of under-diagnosis in PwD requiring an admission to hospital. This low rate of diagnosis may result in inappropriate medications being prescribed to PwD and hospital physicians incorrectly assuming capacity to consent for complex treatments (Timmons *et al.*, 2015).

Our results are in agreement with several pharmacoepidemiological studies, which found a high prevalence of psychotropic medicine use in older hospitalized patients in general (Vidal *et al.*, 2016), and significantly higher levels of psychotropic medications being prescribed to PwD than to those without dementia (Wills *et al.*, 1997; Hartikainen *et al.*, 2003; Hosia-Randell and Pitkälä, 2005; Wergeland *et al.*, 2014). These findings are not surprising due to the ubiquity of BPSD in dementia. One large scale study of the longitudinal course of BPSD in PwD reported a five-year period prevalence of BPSD symptoms of 97% (Steinberg *et al.*, 2008). The most commonly reported symptoms were apathy, depression, and delusions. Of note in this study, many PwD already had BPSD at the time of initial dementia diagnosis. Furthermore, many studies have reported the presence of BPSD in Mild Cognitive Impairment (MCI) (Mariani *et al.*, 2007). There are very recently published criteria for diagnosing Mild Behavioral Impairment (MBI) (Ismail *et al.*, 2016) that describe BPSD as a possible index manifestation of dementia, in advance of measurable cognitive impairment. This is an important conceptual advance in our understanding of dementia, and the prescription of psychotropic medications for changes in behavior or personality may give an indication of an emergent dementia. Furthermore, benzodiazepines are often associated with cognitive decline and dementia (Billioti de Gage *et al.*, 2012); with the implication of causality between the two, although a recent study has questioned this causal association (Gray *et al.*, 2016). An alternative hypothesis is that anxiety can present as the index manifestation of dementia, with benzodiazepines prescribed, and when the underlying dementia ultimately declares itself, the benzodiazepine is labeled as the culprit for cognitive decline (Ismail *et al.*, 2016). The bottom line is that BPSD are fundamental and core features of dementia, and result in greater illness burden, higher caregiver burden, poorer quality of life, higher rates of institutionalization, faster cognitive decline and death, and are associated with greater plaque and tangle burden (Tekin *et al.*, 2001; Shin *et al.*, 2005; Steinberg *et al.*, 2008).

Notwithstanding these important contextual issues, the fact remains that PwD are often excessively and inappropriately prescribed psychotropic medications, and for prolonged periods of time (Banerjee, 2009). We know that in PwD, anti-psychotics significantly increase the risk of stroke and mortality (Maust *et al.*, 2015) and benzodiazepines significantly increase the risk of falls and hip fractures (Hartikainen *et al.*, 2007). Prescription of multiple psychotropic agents results in even greater risk of adverse events (Mojtabai and Olfson, 2010). It is imperative that prescribers and care providers adhere to guidelines, in so far as possible, by utilizing non-pharmacological interventions in the first instance and prescribing anti-psychotics as a last resort, with regular review and trials of withdrawal (Azermai *et al.*, 2012). There is evidence to support the use of non-pharmacological interventions in managing BPSD (Cabrera *et al.*, 2015); however, better quality trials are required in this area.

The prevalence of anti-psychotic usage in the pharmacoepidemiological studies mentioned above ranged from 5% to 43% in those with dementia, highest in studies looking at institutionalized patients. In comparison, the prevalence of anti-psychotic usage in PwD in our study, where 91% of patients were admitted from a home environment, was 14%, lower than a previous study of home-dwelling older people (33%) (Hartikainen *et al.*, 2003). This probably reflects the high rate of undiagnosed cases in our study, with only 35.5% having a prior diagnosis. The rates of prescribing in our study population with known dementia was 28%, similar to that found in the study by Hartikainen *et al.* The INAD study conducted in

2013 found that 41% of PwD were prescribed anti-psychotic medications during their admission in Irish hospitals, and also found poor levels of documentation of mental health assessment and drug indication (de Siún *et al.*, 2014; Gallagher *et al.*, 2016). This figure is much higher than what we found in our study, and may reflect the purposeful selection of patients for the audit who had an explicit diagnosis of dementia and a longer length of stay, thereby potentially representing a much frailer sub-population of PwD. Nonetheless, this high figure is still alarming, considering the same audit conducted in England and Wales in 2012–2013 (Royal College of Psychiatrists, 2013) and Northern Ireland in 2014–2015 (O'Shea *et al.*, 2015) found much lower levels of anti-psychotic prescribing; 18% and 21%, respectively.

We found that patients admitted from a nursing home ($N = 35$) were almost five times more likely to be prescribed an anti-psychotic than those admitted from other home types. The INAD report also found that PwD admitted from nursing homes were significantly more likely to be prescribed an anti-psychotic compared to those admitted from their own home (46% vs. 19%; $p < 0.001$) (de Siún *et al.*, 2014; Gallagher *et al.*, 2016). Similarly, a cross-sectional Finnish nursing home population study found that 43% of residents were prescribed anti-psychotics (Hosia-Randell and Pitkälä, 2005). These findings would indicate that in a busy hospital setting, pharmacists and other healthcare professionals should prioritize PwD, along with patients admitted from nursing homes, for review of their anti-psychotic medications. However, a recent systematic review concluded that there is a distinct lack of such studies conducted in hospitalized dementia patients (Walsh *et al.*, 2016). It is important that any anti-psychotic medication review conducted in a hospital setting involves effective communication with the patient's General Practitioner, carers, and nursing home staff, as it is necessary to know the indication for the anti-psychotic and whether any non-pharmacological intervention or dose reduction had been previously attempted (Mueller *et al.*, 2012). It is also crucial that these community-based care providers are informed of any plans for dose titrations or withdrawals at hospital discharge to prevent the unintended re-commencement of these patients on anti-psychotics.

We did not find any significant differences in terms of anti-cholinergic, deliriogenic, or total number of medications prescribed between the two patient groups. We were surprised by the former finding, as previous studies have reported higher levels of anti-cholinergic prescribing in PwD (Roe *et al.*, 2002). One potential hypothesis is that a greater level of awareness surrounding the risk of cognitive decline with these agents has resulted in more careful prescribing in PwD. However, a repeated cross-sectional study conducted in Scotland found that despite the increasing evidence surrounding the adverse effects of anti-cholinergics, exposure to these agents in the elderly has actually increased in recent years (Sumukadas *et al.*, 2013). We were unable to find literature on the prevalence of deliriogenic medication usage in PwD, thus our *a priori* hypothesis on this topic was purely speculative, based on the knowledge that the PwD in the study had more co-morbidities than their peers. Further research should be conducted to investigate the consequences of deliriogenic prescribing in PwD. The evidence on medication burden in PwD is mixed, with some studies finding PwD are prescribed more (Andersen *et al.*, 2011) and others finding they are prescribed less medications (Schmader *et al.*, 1998) than people without dementia. The discrepancies may relate to population differences between the studies.

Our results differ from previous findings in that we did not detect any significant differences in prescribing patterns of cardiovascular agents between those with and without dementia, whereas previous studies found that PwD were prescribed significantly less of these agents (Wolf-Klein *et al.*, 1988; Wills *et al.*, 1997). One study found that PwD had less co-morbidities than those without dementia (Wolf-Klein *et al.*, 1988). Another group suggested that people without cardiovascular disease may live longer and thus develop dementia without requiring cardiovascular agents (Wills *et al.*, 1997). Given the known links between cerebrovascular disease and dementia, we would suggest that reduced cardiovascular medication prescribing may have resulted from practitioners reducing non-essential medications, such as statins, in older, frailer PwD, especially in more advanced disease. Our cohort of PwD, where 64.5% had no previous diagnosis, probably reflects true prescribing rates without any bias from prescriber's dementia status knowledge. Our analysis shows that drug use by patients with and without dementia was relatively similar for all groups of medications, once age, sex, and co-morbidity were considered, except for nervous system medications.

Strengths and limitations

The main strength of this research was the large number of patients recruited into this multi-centered trial and the vast amount of rich data that were collected from each patient allowing us to

tease apart effects of dementia from confounding factors such as age, sex, and co-morbidity.

The main limitation of this study is due to the retrospective nature of the medication analysis, so that it was not possible to resolve any ambiguous medication data entries. However, the quality of data collection was quite high and this ambiguity rarely occurred. Second, as the study is observational, it is not possible to draw any conclusions on causality, as dementia or cognitive impairment may have been the cause of or potentially even the result of differences in medication usage between the two patient groups. Third, the lack of information on strength, quantity, and duration of medication usage is a limitation to our study. It would have been interesting to investigate the differences in dosing within and between the two patient groups, as toxicity with anti-psychotics, for example, is largely dose-dependent (De Hert *et al.*, 2012). Finally, as the study was conducted in only one county in Ireland, the findings may not be representative of the entire older Irish population. However, as the demographic profile of Cork County is relatively similar to that of the rest of the country, we believe these results may possibly be representative of the entire older Irish population.

Conclusion

Psychotropic drug use and polypharmacy is highly prevalent, and dementia is under-diagnosed among older Irish hospitalized patients. PwD are more likely to be prescribed anti-psychotics, anti-depressants, anxiolytics, and anti-dementia drugs. PwD are also more likely to be exposed to psychotropic polypharmacy. These differences in prescribing patterns may be largely attributed to BPSD in dementia, and NPS in pre-dementia clinical syndromes like MCI and MBI. Longitudinal research is required to assess the long-term impact that medication usage or non-usage has on the development of dementia in older people and also to assess the impact that a diagnosis of dementia has on the physician's prescribing patterns. High quality trials of multi-disciplinary team medication reviews should be conducted in the acute care setting, targeting older patients at high risk of potentially inappropriate prescribing of anti-psychotics, namely PwD and those admitted from nursing homes.

Conflict of interest

None.

Description of authors' roles

Study concept and design: KAW, NOR, SB, JB, DM, ST. Acquisition of Data: KAW, NOR, ST. Analysis and Interpretation of data: KAW, NOR, SB, ST. Preparation of paper: KAW. Critical Review of paper: NOR, SB, JB, DM, ST. Final approval of version to be published: KAW, NOR, SB, JB, DM, ST.

Acknowledgments

The original Cork Dementia Study was supported by the Health Research Board grant number HRA HSR/2011/4. This research was funded by the Health Research Board and Atlantic Philanthropies, a limited life foundation, and was conducted as part of the SPHeRE Programme under Grant No. SPHeRE/2013/1. The investigators were solely responsible for the design, planning, conducting, interpretation, and publication of this study and the funding sources did not participate in such. We gratefully acknowledge all the researchers, staff, and patients who were involved in the original Cork Dementia Study. We also acknowledge the assistance of Dr Tony Fitzgerald for his help with STATA, Mr David O'Riordan for proof-reading the paper and Dr Maire O'Dwyer for her help with defining psychotropics.

Supplementary material

To view supplementary material for this paper, please visit http://dx.doi.org/.10.1017/S1041610216001307

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