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doi:10.1089/jpm.2009.0365

JOURNAL OF PALLIATIVE MEDICINE
Volume 13, Number 6, 2010

DOI: 10.1089/jpm.2009.0365

Anti-Cholinergic Load, Health Care Utilization, and Survival in People with Advanced Cancer: A Pilot Study

Meera Agar, M.P.C., FRACP,[1–3] Timothy To, FRACP,[4] John Plummer, B Pharm., Ph.D., AStat,[5] Amy Abernethy, M.D.,[1,6] and David C. Currow, M.P.H., FRACP[1]

Abstract

Introduction: Anti-cholinergic medications have been associated with increased risks of cognitive impairment, premature mortality and increased risk of hospitalisation. Anti-cholinergic load associated with medication increases as death approaches in those with advanced cancer, yet little is known about associated adverse outcomes in this setting.

Methods: A substudy of 112 participants in a randomised control trial who had cancer and an Australia modified Karnofsky Performance Scale (AKPS) score (AKPS) of 60 or above, explored survival and health service utilisation; with anti-cholinergic load calculated using the Clinician Rated Anti-cholinergic Scale (modified version) longitudinally to death. A standardised starting point for prospectively calculating survival was an AKPS of 60 or above.

Results: Baseline entry to the sub-study was a mean 62 ± 81 days (median 37, range 1–588) days before death (survival), with mean of 4.8 (median 3, SD 4.18, range 1 – 24) study assessments in this time period. Participants spent 22% of time as an inpatient. There was no significant association between anti-cholinergic score and time spent as an inpatient (adjusted for survival time) ($p = 0.94$); or survival time.

Discussion: No association between anti-cholinergic load and survival or time spent as an inpatient was seen. Future studies need to include cognitively impaired populations where the risks of symptomatic deterioration may be more substantial.

Introduction

Medications with cholinergic effects have been associated with significant morbidity including unpleasant symptoms, accelerated functional decline, delirium (and its associated poor outcomes), cognitive impairment and risk of drug interactions.[1–9] Little is known about the impact of prescribing anti-cholinergic medications on outcomes pertinent to palliative care for people with advanced cancer.

Anti-cholinergic load associated with medications has been documented to increase as death approaches, mainly from the addition of symptom control medications.[7] This is in the context of an average of five or more medications per person in people with advanced disease, both for symptom control and for comorbid conditions.[10,11] In those with advancing cancer, it is also postulated that specific tumour-derived factors, cytokines, and other endogenous substances may have anti-cholinergic activity, and therefore also add to anti-cholinergic burden.[12,13] There are similar processes in acute illnesses that generate a significant cytokine response.

The adverse effects of anti-cholinergic medication such as dry mouth, dizziness, acute cognitive impairment and constipation can iatrogenically increase symptom burden, which is especially problematic in people with advancing cancer when symptom burden is already high.[6–8] In a prior study in a larger palliative care population derived from the same randomised controlled trial (RCT), total anti-cholinergic load was significantly associated with lower levels of global function, difficulty concentrating and dry mouth.[7]

Many symptom-specific medications meet also Beers' criteria as high risk medications in older adults, and are associated with additional adverse effects from drug-drug

[1]Department of Palliative and Supportive Services, Flinders University, Adelaide, Australia.
[2]Department of Palliative Care, Braeside Hospital, New South Wales, Australia.
[3]South West Sydney Clinical School, University of New South Wales, New South Wales, Australia.
[4]Southern Adelaide Palliative Services, Repatriation General Hospital, Adelaide, Australia.
[5]Department of Anaesthesia and Pain Management, Flinders Medical Centre, Adelaide, Australia.
[6]Division of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, North Carolina.
Accepted January 26, 2010.

interactions (in particular in the elderly, those with multiple comorbidities, and in particular tumour types e.g., brain tumours).[10,14] Medications that are "high risk" on Beers' criteria can lead to increased risks of hospitalization and premature mortality.[15–17]

To date there has been no study of people with advanced cancer exploring the association between anti-cholinergic medication burden and health service utilisation or survival outcomes.[15–17] The aim of this sub-study was to explore associations of anti-cholinergic load in people with advanced cancer on health service utilisation and survival. The null hypotheses were that anti-cholinergic load was not associated with increased health service utilisation nor decreased survival in people with advanced cancer.

Methods

Setting

Southern Adelaide Palliative Services is a specialist metropolitan palliative care programme, which provides inpatient care, community and outpatient visits, nursing home and hospital consultations, and also offers volunteer, complementary care and bereavement services. It serves a population of 350,000 people over an area of more than 750 km^2 providing services in both the public and private sectors. Palliative Care Unit inpatients receive direct clinical care, while all other care is in conjunction with the person's principal clinical team or their general practitioner and community nursing services. The Australian healthcare system provides universal insurance that can be supplemented by private insurance and co-payments for many community services.

Study design

This sub-study is a secondary analysis of participants in the Palliative Care Trial (PCT). The PCT was a prospective $2\times2\times2$ factorial unblinded cluster RCT of educational outreach visiting and case conferencing in people with advanced disease. The full clinical trial methodology has been detailed elsewhere.[18,19] The PCT enrolled 461 consenting participants and their general practitioners between April 2002 and June 2004. The inclusion criteria were patients with any form of pain in the three months preceding assessment. Exclusion criteria included: place of residence outside the geographic area, death expected within 48 hours of referral, and Folstein Mini-Mental Status Examination (MMSE)[20] score ≤ 24 at baseline assessment, unless there was a suitable proxy who could provide consent.

Ethics approval

This trial was approved by all twelve relevant independent HRECs and IRBs including the Australian Department of Veteran Affairs and Health Insurance Commission, Canberra, Australia. The trial is registered with the ISRCTN81117481 (http://www.controlled–trials.com/isrctn/trials/81117481/0/81117481.html).

Participants for secondary analysis

The inclusion criteria for the secondary analysis were:

1. a diagnosis of cancer;
2. known date of death;
3. Australia – modified Karnofsky Performance Scale (AKPS) score at initial assessment of 60 or above; and
4. AKPS score fell to below 60 at some time point during longitudinal follow-up.

The Australia–modified Karnofsky Performance Scale (AKPS) is a functional scale where 100 equates with full function, a score less than 70 requires increasing support from other people, less than 30 is totally dependent on others' help, and 0 is dead.[21] In order to standardise a common starting point for the calculation of survival in this population, only people whose Karnofsky score was 60 or above at initial assessment were included in the analyses. The baseline time point was defined as the first visit at which AKPS score was below 60. This gave a homogenous starting point from prospectively collected data for the subsequent health service utilisation and survival trajectories to be considered given the widely varying time-points at which referral to specialist palliative care services can occur before death.

Assessments

All participants enrolled in the PCT trial underwent community-based reviews at initial referral, fortnightly for 3 months, and then at least monthly until death. A list of regular medications was recorded at each visit (generic drug name, dose, route of administration, indication, frequency and pattern of use). Data excluded medications used on an as-needed basis, short course medications such as antibiotics, intravenous chemotherapy, and agents with no Australian Therapeutics Code (complementary or alternative therapies), given the latter's wide variation in labelling and poorly characterised anti-cholinergic loads.[10]

Data collection

Baseline assessments included demographic data (age, gender, primary diagnosis, co-morbid diseases, and date of referral to the service). At each visit the presence or absence of symptoms including dry mouth, constipation, hallucinations and confusion was recorded using clinical assessment and the Memorial Symptom Assessment Scale.[22] Functional assessment was made at each review using the AKPS. Quality of life was measured at each visit using the McGill Quality of Life Scale.[23]

Calculation of total anti-cholinergic score, survival, and health service utilisation

The Clinician Rated Anti-cholinergic Scale (modified version) was used.[24,25] Each medication is rated from 0 (no known anti-cholinergic effect) to 3 (marked anti-cholinergic effects).[24,25] Total anti-cholinergic score (baseline) was calculated as the sum of anti-cholinergic scores for each medication being received regularly at the baseline time-point. For purpose of analysis total anti-cholinergic score at baseline was divided into three strata from summed scores with approximately equal numbers of patients: 0–2, 3–5, and 6–9. The three strata of anti-cholinergic scores were entered into models as categorical variables. Survival was calculated as the number of weeks from the baseline time point (crossing AKPS score of 60 as functional decline occurred) until death. Health service utilisation was obtained by summing all

length-of-stay times (in days) that occurred after the baseline time point. For descriptive purposes, health service utilisation was divided by time from baseline to death for each participant to give the proportion of time spent as an in-patient.

Data analysis

Demographic data of subjects who were included in this sub-study and those who were not were compared by chi-square test for categorical data or Mann-Whitney U-test for continuous and ordinal data.

Analysis of service utilisation was performed using generalised linear models, with a gamma error distribution and logarithmic link function. The dependent variable was number of days spent as an in-patient; in order to remove the influence of survival time, the logarithm of time from baseline to death was included as an offset. Kaplan Meier survival curves were compared using a logrank test. Analyses were conducted using the software package Stata version 10 (Stata Corporation, College Station, TX 2007).

Results

Participants

Participants in the RCT did not differ by age, gender, marital status, or level of education from the whole population referred to the palliative care service during the same period (data not shown), but did more commonly have cancer (RCT cohort 91% vs. whole service 85%), and lived longer from the time of referral to palliative care (median 87 days; range 1–833), compared with the whole service (median 48 days; range 0–1642). This longer survival is consistent with the exclusion of patients expected to die within 48 hours of enrolment, which was used as a means of excluding participants from the whole cohort study.

For the RCT (from which this sub-study population was derived), 461 people were enrolled (50% males) with an average age of 71 years (SD 12). Two hundred and eighty two participants were married or in a *de facto* relationship. Ninety per cent lived in their own home, and 91% had cancer as their life-limiting illness (Table 1). Baseline entry to the main study was a mean 107 ± 103 days (median 93; range 11–752) days before death.

For this sub-study of the RCT population ($n = 112$), the median Australian-modified Karnofsky Performance Status scale was 60. The sub-study participants were similar to the whole cohort, apart from all having a diagnosis of cancer (as a specific inclusion criterion), having a higher AKPS (value; $p < 0.001$) at referral and higher percentage of people in the stable phase ($p = 0.006$) (62) consistent with better performance status. The 9% with non-cancer life limiting illness excluded in this substudy had predominately cardio-respiratory disease.

Participant flow (using CONSORT criteria) of participants for the larger RCT is in Fig. 1.

Participant characteristics in this sub-study

Baseline entry to the sub-study was a mean 62 ± 81 days (median 37, range 1–588) days before death (survival). The mean time from last assessment until death was 23 days (SD 23 days; median 16 days; range 1–241 days), and the assessment before this was a mean of 29 days earlier (SD 22; median

Table 1. Baseline Demographic and Clinical Characteristics for All Participants and Sub-Study Participants on Referral to a Randomised Controlled Trial on Palliative Care Service Intervention

Characteristic		n = *434* *(all participants)*	n = *322* *(not in sub-study)*	n = *112* *(sub-study participants)*	p *value* *(two previous columns)*
Age	Mean (SD)	71 (12)	71 (12)	72 (12)	0.22
Gender	Male	216 (50%)	162 (50%)	54 (48%)	0.70
Marital status	Married/De facto	264 (63%)	191 (61%)	73 (66%)	0.36
	Widowed	98 (23%)	71 (23%)	27 (25%)	
	Divorced/Separated	45 (11%)	39 (13%)	6 (5%)	
	Never Married	15 (4%)	11 (4%)	4 (4%)	
Educational level	Didn't complete high school				
	Completed high school	75 (20%)	58 (21%)	17 (17%)	0.45
Folstein Mini-mental status exam (20)	Mean (SD)	28.8 (2.2)	28.7 (2.3)	29.0 (1.9)	0.12
Caregiver status	Has caregiver	350 (93%)	259 (93%)	91 (95%)	0.45
	No caregiver				
Accommodation	Private residence	387 (91%)	285 (90%)	102 (94%)	0.26
	Aged care facility	25 (6%)	20 (6%)	5 (5%)	
	Hospital	13 (3%)	12 (4%)	1 (1%)	
Living arrangement	Lived alone	88 (23%)	70 (24%)	18 (19%)	0.56
	Lived with spouse/Partner only	234 (61%)	173 (60%)	61 (66%)	
	Other person in household	61 (16%)	47 (16%)	14 (15%)	
Performance status (AKPS) (21)	Mean (SD)	64.8 (13.9)	63.4 (14.2)	69.2 (12.2)	<0.001
	Median (range)	70 (20–90)	60 (20–90)	70 (50–90)	
	AKPS <70%	215 (50%)	174 (54%)	41 (37%)	
Phase of palliative care (62)	Stable	217 (58%)	143 (54%)	74 (69%)	0.006
McGill Quality of life (23)	Mean (SD)	6.1 (2.0)	6.0 (2.0)	6.3 (1.9)	0.17

25). The mean length of follow-up after first assessment was 109 days (SD 124, range 1–159). The mean number of study assessments between referral and death was 4.8 (median 3, SD 4.18, range 1 – 24) per participant.

Baseline AKPS and total anti-cholinergic score at first visit AKPS < 60

The distribution of AKPS at the initial assessment (enrolment in study) and anti-cholinergic score at the baseline time point for this sub-study (defined as the first visit at which AKPS score was below 60) are shown in Table 2.

Table 2. Baseline Total Anti-Cholinergic Score and Australian-Modified Karnofsky Performance Status (AKPS) at First Visit Where AKPS was Less Than 60 in 112 Participants

	Score	n	*Percentage (%)*
AKPS	10	5	4.5
	20	8	7.1
	30	9	8.0
	40	16	14.3
	50	74	66.1
Total anti-cholinergic score	0–2	32	28.6
	3–5	47	42.0
	6–9	33	29.5

Association between health service utilisation (proportion of time as inpatient) and total anti-cholinergic scores

Patients spent a mean of 22% (range 0–100%) of their time as an inpatient. The distribution of total length of stay in Fig. 2. Analysis using an unadjusted log-gamma model (scaled for survival time) did not show a significant association between total anticholinergic score and time spent as an inpatient ($p = 0.94$) (Fig. 3).

Survival times

The mean survival time for the 112 participants was 8.9 weeks (SD 11.6, median 5.3, range 0.2 – 84.4).

Association of total anti-cholinergic score with survival

Figure 4 presents a Kaplan-Meier plot showing survival for the 3 categories of total anti-cholinergic scores. A log-rank test demonstrated there was no evidence that survival differed between the 3 groups. The median survival times were approximately 5 weeks in each group.

Discussion

In this study, no association has been demonstrated between anti-cholinergic load and changes in survival or health service utilisation in a population referred to a specialist palliative. It has been previously demonstrated in the setting of a life limiting illness that the total medication load increases as death approaches, with the addition of symptom-specific medication.[10] The biggest contributor to anti-cholinergic scores in a population with advanced cancer is from symptom-specific medications.[7] Prior work has shown that anti-cholinergic load is associated with impaired function, impaired concentration and dry mouth in this population.[7]

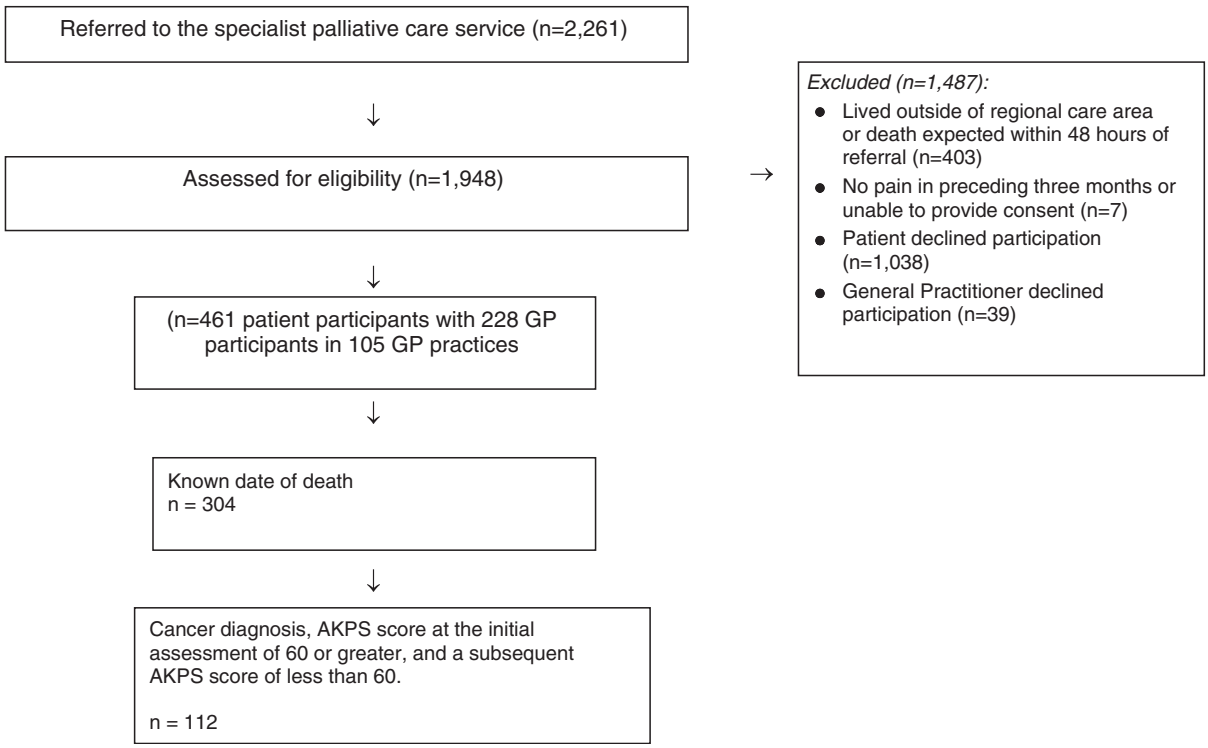

FIG. 1. Patient flow for all participants and sub-study participants on referral to a randomised controlled trial on palliative care service intervention.

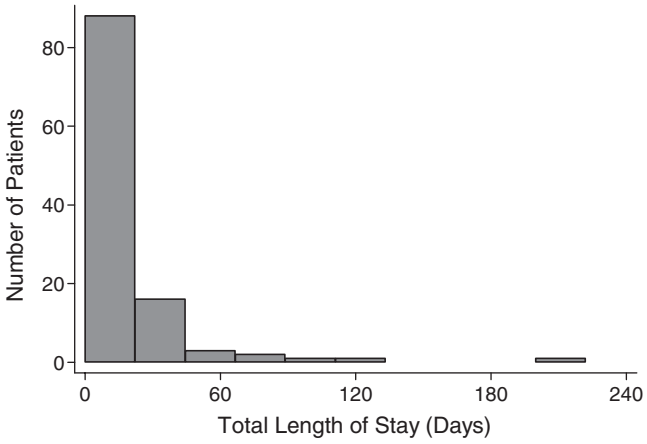

FIG. 2. Distribution of total length of inpatient stays* (n = 112).

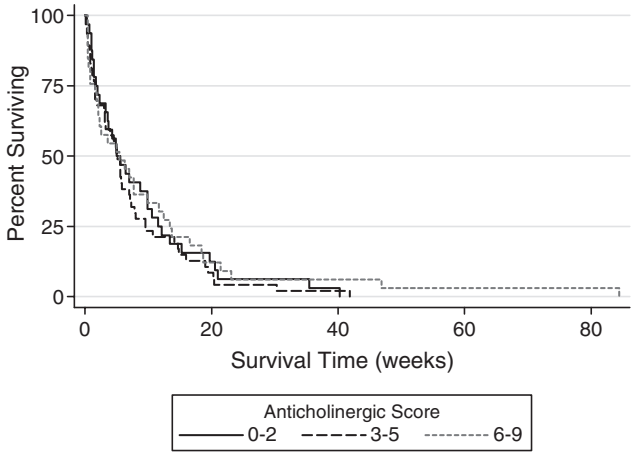

FIG. 4. Kaplan-Meier plot showing survival for the 3 categories of Total Anti-cholinergic scores.

This current analysis has not demonstrated an association with anti-cholinergic load and survival or time as an inpatient.

What other data do these findings support or refute?

Anti-cholinergic medications have been associated with risk of falls, reduced functional status, and impaired motor performance, however this is the context of ambulatory patients in the community over the age of 65.[1–6] In a study of moderately to severely disabled women aged 65 or over and residing in the community (n = 932), anti-cholinergic drug burden was independently associated with greater difficulty in several measures of physical function, after adjustment for age, education and co-morbidities.[5] Another study of well functioning community-dwelling elderly (n = 3075) showed medications with anti-cholinergic effects were associated with poorer physical and cognitive performance after adjusting for socio-demographic factors and co-morbidities.[4]

There is also a link with poor cognitive outcomes, especially in the group with existing cognitive impairment.[4,5,26–32]

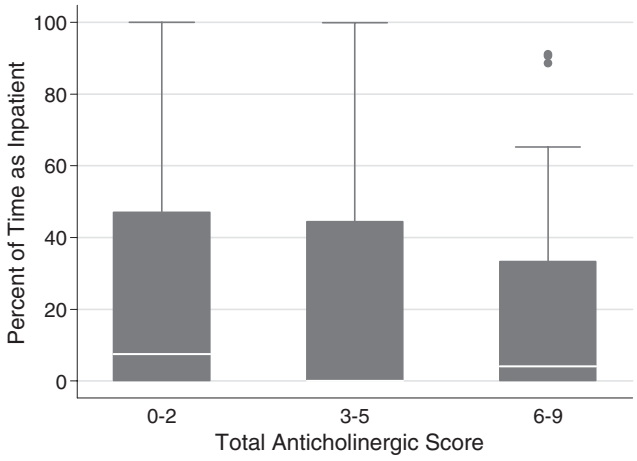

FIG. 3. Association between Health Service Utilisation (percentage of time as inpatient (hours)) and Total Anti-cholinergic score in 112 participants.

Anti-cholinergic medications can precipitate delirium and intensify pre-existing delirium.[8,25,33–40] An episode of delirium is linked to significant morbidity and mortality, and is associated with increased length of hospital stay, institutionalisation, irreversible functional and cognitive decline, and mortality in the elderly.[41–49]

The prevalence of potentially high risk medication prescribing (considering medications more broadly than just those with anti-cholinergic effects) in the infirm (especially the elderly) is high though some improvements have been seen more recently.[50,51] Studies looking at high risk medications in the elderly in acute care, residential aged care or community settings (most often classified by Beers' criteria) have shown contradictory outcomes, with some showing poor outcomes (increased hospitalisation, increased length of stay, adverse drug reactions, risk of institutionalisation, mortality) where as others have not demonstrated this.[15–17,52–55]

Prescribing patterns and outcomes in palliative care have been less well described. In the palliative care population increasing total anti-cholinergic load was associated with decreased functional status, after adjustment for time from death; with contribution from symptom-specific medication to anti-cholinergic load highest in the group with lowest performance status.[7] The population of people with advanced cancer may differ to aged care populations most notably in age (one third of the this population is under 65), more marked cachexia (although levels of sarcopaenia may be similar) and may not be as susceptible to long term treatment related effects. Similiarities include polypharmacy, co-morbidities and progressive functional impairment.

Strengths

By anchoring the sub-study population using prospectively collected data for the time at which a predetermined threshold of functional status was reached in order to define inclusion, this sub-study allows the analysis of survival in a palliative population despite widely varying times before death at which referral to the specialist service occurs. By doing this, Kaplan Meier curves can be generated in a population with advanced disease. This is an important evolution in analysis

moving away from death as the only anchor point to standardise in palliative care analyses that can be used in palliative care studies. Such a process can be employed with different thresholds of functional status on any prospectively collected data.

Limitations—sample

Not everyone with life-limiting cancer is referred to a specialist palliative care service and, in general, people with more complex needs are the people referred.[56] Given that people with prevalent delirium at enrolment to the larger RCT were excluded from participation and that at least a sub-set of these people would have developed delirium as a consequence of a high anti-cholinergic load, it is likely that the current sub-study will underestimate the consequences of raised anti-cholinergic load. The requirement for pain to be present in preceding three months also may alter anti-cholinergic load due to prevalence of analgesic medication use.

People with cognitive impairment (who are also more at risk of the consequences of raised anti-cholinergic load) are not represented in the data. Both exclusions will have potentially increased the survival and decreased the health service utilisation (number of admissions, length of those admissions) in this sub-study.

Incident delirium following a previously resolved delirium occurs in up to 30% of people with advanced cancer. Resolution of the second episode of delirium is less likely and has poorer outcomes; including increased mortality.[57,58]

This pilot sub-study had a relatively small sample size and hence is exploratory in nature. It is not adequately powered to detect differences in health service utilisation or survival, but of note, the trends seen make it unlikely that any difference found in a much larger study is likely to be clinically significant.

The choice of AKPS as the threshold for the entry to the sub-study was not entirely arbitrary. This choice needed to balance the number of people who would be eligible across the disease trajectory (a very low AKPS) with the longest possible time for follow-up after entry to the study (a high AKPS). As such, crossing the threshold of 60 was chosen as the compromise between these two extremes. The inclusion of only 112 out of 434 participants suggests that almost three out of four people have significant functional impairment at the time of referral to specialist palliative care.

Limitations—measures/data

Medications used intermittently were not included. Such medications may contribute to side-effects experienced from an acutely increased anti-cholinergic load. Only baseline medications were used for total anti-cholinergic load and this will underestimate the documented increase in anti-cholinergic load as symptom control medications are added in.

Several methods of calculating anti-cholinergic drug burden have been suggested, including calculating anti-cholinergic burden score.[59] The most comprehensive method currently available is the Clinician Rated Anti-cholinergic Scale – modified version[24,25] which gives medications one of four ratings:

Level 0 - no known anti-cholinergic properties;
Level 1 - potentially anti-cholinergic as demonstrated by receptor binding studies;
Level 2 - clinically significant anti-cholinergic effects are sometimes seen, usually at excessive doses; and
Level 3 - marked anti-cholinergic effects.

This allows calculation of a total anti-cholinergic score at each time point for each participant.[24,25] This classification was developed using reported anti-cholinergic effects in the literature, available laboratory data, and ratings of 3 independent geriatric psychiatrists.[25] The benefits of using the Clinician Rated Anti-cholinergic Scale – modified version[24,25] is that is characterizes medications based on anti-cholinergic potency, and includes a broader list than just those most frequently recognized as having anti-cholinergic effects, Its limitations include lack of dose weighting, assumption of anti-cholinergic effects being additive (not synergistic) and linear (that is, one medication with score of 3 is equivalent to three medications each with score of 1).[60] A more sophisticated measure which accounts for dose, frequency and duration of use may be needed to understand the totality of adverse outcomes attributable to anti-cholinergic load from medications. A gold standard that would be difficult to achieve would be to measure serum levels of anti-cholinergic activity longitudinally in this population.

Adjustment for other prognostic factors which independently predict survival in advanced cancer was also not performed but will be important in prospective work. These include presence of dyspnoea, anorexia and delirium, clinicians' predictions of survival, total white cell count and the proportion of lymphocytes in the total white cell count.[61]

Future directions: Practice and policy

Given that it is assumed that the cumulative anti-cholinergic load could be a predictor of toxicity in people with advanced cancer, the previously demonstrated associations between raised anti-cholinergic scores, impaired function and adverse symptoms warrants every effort to reduce anti-cholinergic load by medication substitution (for a medication with no or lesser anti-cholinergic load) or deletion of medications no longer required for managing co-morbid conditions that are now inactive. A lack of impact on survival is in this sub-study and is consistent with some studies in the aged care populations, despite other studies showing a relationship between medication burden and mortality.[15–17, 52–55]

Future direction: Research

Future research needs to prospectively follow a population of people with advanced cancer, including those with prior cognitive impairment and those with both prevalent and incident delirium to further delineate effects of anti-cholinergic load. Models of prognosis anchored at performance status may also provide more helpful ways of estimating survival prospectively, with the ability to raise the threshold for entry into a subsequent study to AKPS 70 or 80 in order to increase the likelihood of detecting events over a longer period of observation.

Acknowledgments

1. Rural Health and Palliative Care Branch of the Australian Department of Health and Ageing (Canberra, Australia).
2. Ian Potter Foundation (Melbourne, Australia).

3. Cancer Council South Australia (Adelaide, Australia).
4. Doris Duke Charitable Foundation (New York City, New York USA).

Author Disclosure Statement

No conflict of interest and no competing financial interests exist.

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Address correspondence to:
Meera Agar, M.P.C., FRACP
Department of Palliative and Supportive Services
Flinders University
700 Goodwood Road
Daw Park
Adelaide 5041
Australia

E-mail: meera.agar@sswahs.nsw.gov.au