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Association between objectively measured physical activity and opioid, hypnotic, or anticholinergic medication use in older people – data from the Physical Activity Cohort Scotland study

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Abstract

Background

Centrally acting medications cause cognitive slowing and incoordination, which could reduce older people's physical activity levels. This association has not been studied previously.

Objectives

To examine the association between opioid, hypnotic and anticholinergic medication, and objectively measured physical activity, in a cohort of older people.

Methods

We used data from the Physical Activity Cohort Scotland, a representative cohort of community-dwelling older people aged 65 and over who were assessed at baseline and again 2-3 years later. Objective physical activity was measured using Stayhealthy RT3 accelerometers over 7 days. Baseline medication use (opioid use, hypnotic use, modified anticholinergic risk score [mARS]) was obtained from linked, routinely collected community prescribing records. Cross-sectional and longitudinal associations between baseline medication use and both baseline activity and change in activity over time were analysed using unadjusted and adjusted linear regression models.

Results

310 participants were included in the analysis; mean age 77 (SD 7) years. No association was seen between baseline use of any medication class and baseline physical activity levels in unadjusted or adjusted models. For change in activity over time, there was no difference between users and non-users of hypnotics or opioids. Higher anticholinergic burden was associated with a steeper decline in activity over the follow up period (mARS=0: -7051 counts/24h/yr; mARS=1-2 -15942 counts/24h/yr; mARS>=3 -19544 counts/24h/yr; p=0.03) and this remained robust to multiple adjustments.

Conclusion

Anticholinergic burden is associated with greater decline in objectively measured physical activity over time in older people, a finding not seen with hypnotic or opioid use.

Key points

- Few studies have examined the association of medication use with habitual physical activity in older people
- Use of opioids, hypnotics and anticholinergics was not associated with objectively measured physical activity levels in cross-sectional data
- Increasing anticholinergic burden was associated with more rapid decline in objectively measured physical activity levels over time

1. Introduction

Regular physical activity is known to be associated with a host of health benefits, and is an important determinant of health and function in later life. Physical activity helps to protect against cardiovascular disease, diabetes, cancer and dementia [1], as well as protecting against the decline in physical function that often accompanies old age, and which leads to falls, hospitalisation and care home admission. It is therefore particularly concerning that only 7% of men and 4% of women over the age of 75 years in the UK reach current physical activity recommendations [2,3]. Interventions to improve habitual, everyday physical activity in older people have had only limited success to date, suffering from suboptimal efficacy, low uptake and low adherence [4,5]. In order to develop better interventions to improve PA in older people, a more complete understanding of the relationships between health, disability and activity in older people is desirable, in addition to the interplay between these factors and other social, psychological and environmental factors.

One important area that has received little attention to date is the relationship between medication use and physical activity in older people [6]. The majority of older people suffer from multimorbidity, and hence take multiple medications [7]. Just as some diseases may interfere with the ability to undertake physical activity (for instance arthritis, heart failure or lung disease), it is plausible that some medications may also interfere with the ability to undertake physical activity. In particular, medications that impair brain function and cause drowsiness or confusion might be expected to inhibit both the desire and ability to undertake physical activity [8].

Such medications include sleeping tablets, some antidepressants, opioid painkillers, but also importantly medications with anticholinergic side effects. Anticholinergic medications encompass all medications with action at acetylcholine receptors, whether such effects are intended or are 'off-target' effects. The majority of side-effects are mediated via multiple muscarinic receptor subtypes, and include postural instability, cognitive impairment, dry mouth, constipation, blurred vision and

urinary retention. These side effects are shared by a wide range of medications used by older people, and the burden of anticholinergic action can be quantified using readily-available scoring systems. Existing research has already suggested that increased anticholinergic medication burden is associated with an increased risk of earlier death and a higher chance of memory impairment in older people [9,10]; higher cumulative exposure to anticholinergic agents is associated with a higher risk of a future diagnosis of dementia [11]

In this paper, we analyse data from the baseline and follow up waves of the Physical Activity Cohort Scotland (PACS) with the aim of describing a) the cross-sectional association between opioid, hypnotic and anticholinergic medication use and physical activity, and b) the association between opioid, hypnotic and anticholinergic medication use and change in physical activity over time, in older people.

2. Methods

2.1 Study population

The Physical Activity Cohort Scotland (PACS) is a representative sample of nearly 600 community dwelling older people from Tayside, Scotland. The cohort was sampled to ensure good representation of those aged 80 and over, as well as including socially deprived individuals. At baseline, physical activity was measured objectively using 7-day triaxial accelerometry; a wide range of psychological, behavioural and environmental information was also collected at baseline. The sampling methods and baseline results have been described in detail previously [2]. The measurements were repeated on approximately 350 cohort members two to three years later [12], when consent was also obtained for linkage of PACS data to other routinely collected healthcare data.

Written informed consent was obtained from all participants at baseline and at follow up; the study was approved by the Tayside Committee on Medical Research Ethics (09/S1401/57 and 12/ES/0016). The study conformed to the principles of the Declaration of Helsinki.

2.2 Data linkage

Data collected during the baseline and follow up study visits were linked to routinely collected clinical data for the participants giving consent for this process at the follow up visit. Consent was not sought for this process at the baseline visit, hence not all participants could have study data linked to routinely collected clinical data. Data linkage was performed by the Health Informatics Centre (HIC), University of Dundee, and the linked, de-identified dataset was stored within the HIC Safe Haven environment to ensure data security and confidentiality. All analyses were performed within the Safe Haven environment.

Sources of routinely collected data were linked via the 10-digit Community Health Index (CHI) number assigned to all inhabitants of Scotland. Previous diagnoses of comorbid disease were derived from discharge diagnoses held on the SMR01 (Scottish Morbidity Register 01) register, which holds a record of all Scottish hospital discharges. A previous diagnosis of cancer within the 5 years prior to study entry (excluding basal cell carcinoma of the skin) was derived from SMR06 (Scottish Morbidity Register 06), which holds records of all Scottish cancer diagnoses. A diagnosis of diabetes mellitus prior to study entry was obtained from the Scottish Care Information – Diabetes Collaboration (SCI-DC) database. Community prescribing data, comprising encashed prescriptions, were also linked and used to derive medication use.

2.3 Measurement of physical activity

Physical activity at baseline and follow up visits was measured using the RT3 triaxial accelerometer (Stayhealthy Inc, Monrovia, California, USA) worn on the waistband over the same hip during waking

hours for a seven-day period. Summed vector magnitude activity counts were recorded each minute for 7 days. 24 hour periods commenced at midnight; the partial data from the first and last day was therefore discarded leaving a maximum of 6 periods of 24 hours for analysis. Days with less than 6 hours of recorded activity data were omitted from analysis. A Freepost envelope was provided in which to return the accelerometer. Participants were instructed to remove the device at bedtime, and also not to wear the device during bathing and showering. The RT3 has previously been validated in a number of different ways: it shows adequate test-retest reliability, it has been shown to discriminate walking from sedentary activity in older people, and it is responsive to interventions designed to increase physical activity[13-15].

2.4 Measurement of medication use

Data on prescriptions dispensed by community pharmacies are collected and held by HIC; these data cover all community-dispensed prescriptions in the Tayside area, but do not cover hospital-dispensed prescriptions. We defined baseline medication use as any prescription in each category (opioids, hypnotics, anticholinergics) in the 90 days prior to the date of the baseline PACS visit. Opioid prescriptions were defined as any prescription from category 4.7.2 of the British National Formulary; hypnotic prescriptions were defined as any prescription from category 4.1 of the British National Formulary, with the exception of melatonin and sodium oxybate. The modified anticholinergic risk score (mARS) was calculated using the weightings developed by Rudolph et al [9] and modified by Sumukadas et al [16]. A mARS score of 0 denotes no or limited anticholinergic potential; 1 = moderate potential, 2 = strong potential and 3 = very strong potential. Although lacking data on dose that accompanies some other anticholinergic scales, the ARS has been used in several previous population based studies and has been shown to be strongly associated with impaired cognitive and functional outcomes[17-19].

2.5 Covariates

Three categories of covariates were selected for use in adjusted models. Variables that had previously been shown to be independently associated with baseline physical activity in the PACS cohort [2] were used: SF-36 physical function, number of people one can turn to in a crisis, high self-efficacy (perceived behavioural control from Theory of Planned Behaviour questions), along with age, sex and decile of deprivation obtained using the Scottish Index of Multiple Deprivation (SIMD) [20]. Categories of self-reported comorbid disease recorded by the Older People and Active Living (OPAL) questionnaire [21], self-reported chronic pain, and self-reported falls in the year prior to study enrolment were obtained from the baseline wave of data collection. We added measures of comorbid disease, but did not include measures of environment from baseline as these were not significantly associated with baseline activity counts in our previous analysis. Additional comorbid disease diagnoses were obtained from ICD-10 coded hospital discharge diagnoses prior to study enrolment, using linked data obtained from the SMR01 database. ICD (International Classification of Disease) version 10 codes used to derive these diagnoses were: Myocardial infarction: I21, I22; Stroke: I61, I63, I64; Heart failure I50; Chronic obstructive pulmonary disease: J41, J42, J43, J44, J47. Objectively diagnosed cancer and diabetes mellitus were derived from SMR06 and SCI-DC registers as described above.

2.6 Statistical analysis

Baseline activity data were known to be highly skewed, and are thus presented as medians with interquartile ranges. Unadjusted comparisons of baseline activity between users and non-users of each medication class were made using Mann-Whitney U test for two-category comparisons, and Kruskal-Wallis test for three-category comparisons. Change in activity levels with time was expressed as change per year of follow up; these data were normally distributed and analysis of covariance (adjusting for baseline activity count) was used to compare groups.

In order to adjust for baseline covariates, multivariable linear regression models were run, using log-transformed activity count as the dependent variable. A separate set of models were run using change

in activity count between baseline and follow up as the dependent variable. Each model included all three medication categories. For each dependent variable, three models were run – firstly adjusting for factors known from previous work to be associated with activity counts in this cohort (age, sex, deprivation, number of people nearby to turn to, perceived behavioural control, SF-36 physical function), secondly adding baseline comorbid disease, chronic pain and falls (as a proxy for frailty), and thirdly, adding in the number of medications remaining after accounting for opioids, anticholinergics and sleeping medications, as a measure of overall medication burden. All analyses were conducted using SPSS v22 (IBM, New York, USA) and a two-sided p value of <0.05 was taken as significant for all analyses.

3. Results

A total of 584 participants were recruited at baseline; 339 of these underwent the follow up assessment, and of these, 310 had complete data and form the group analysed here. Details of these 310 participants at the baseline study visit are shown in Table 1.

Table 2 depicts unadjusted analyses contrasting activity levels and change in activity during follow up for baseline users of opioids, hypnotics and anticholinergics. No significant difference was seen in baseline activity counts between users and non-users of any medication class, but participants with higher baseline mARS scores exhibited a greater decline in objectively measured physical activity between baseline and follow up.

Table 3 shows the association between baseline activity counts and medication use after adjustment for covariates; Table 4 similarly shows adjusted analyses for the association between baseline medication use and change in activity counts. Similar to the unadjusted analyses, no significant difference was seen in baseline activity counts between users and non-users of any medication class,

but higher baseline mARS remained significantly associated with greater declines in physical activity with time, even after adjusting for all covariates.

To further explore the interaction between self-reported pain, opioid use and baseline activity levels, we calculated median baseline activity counts in a two-by-two table (Table 5). Self-reported pain was associated with lower activity levels, but no significant interaction was found between self-reported pain and opioid use on baseline activity levels (p for interaction=0.31)

4. Discussion

Our analysis found no significant association between objectively measured physical activity and three important classes of medications commonly used in older people. However, individuals with a higher anticholinergic burden showed a greater decline in their physical activity levels over a 2-3 year follow up, and this finding persisted after adjustment for multiple sociodemographic variables and comorbidities.

Dissecting out causality from observational studies, even with longitudinal follow-up, is not possible. Although our findings suggest that use of anticholinergic medications might contribute to a decline in PA, it is equally possible that anticholinergic medication use is a marker for other factors (particularly comorbid disease) that drive the decline in PA. However, the association between anticholinergic medication and decline in PA was robust to adjustment not only for a series of comorbidities, but also for the number of medications, which can be viewed as a surrogate for total burden of comorbidity. Anticholinergic medication use has been associated with a range of adverse consequences; a recent systematic review highlights associations between anticholinergic use and decline in activities of daily living and decline in cognitive function [22], and a recent large case-control study found an increased risk of dementia with higher cumulative exposure to anticholinergic agents [11]. These results are consistent with our findings; direct effects of anticholinergic medications on cognition could explain

some of the reduction in PA seen in the current analysis. Furthermore, anticholinergic medications are associated with worse balance and more falls[23]. The mechanism for this finding is unclear but could be due both to a reduction in processing speed, and to promotion of cerebral vasculopathy and consequent white matter changes. Fear of falls may dissuade individuals from undertaking PA. Finally, anticholinergic burden may be associated with a higher incidence of new cardiovascular events[24]; this would again be expected to reduce physical activity.

Given the profound effects that hypnotic agents are known to have both on cognitive function and on falls risk [25], it is perhaps surprising that use of such agents was not associated with either baseline PA or a decline in PA when compared to non-users. Numbers taking this medication class were small, limiting the ability of the analysis to detect a significant difference, and it is noteworthy that users had both a non-significantly lower level of PA at baseline and a non-significantly greater decline in PA during follow up. The lack of significance may therefore be due to a lack of statistical power rather than absence of a true association. It is also possible that those at highest risk of adverse effects from hypnotics are not prescribed these agents; recent years have seen a focus both on limiting initiation of these agents and in deprescribing these agents [7], particularly amongst older people with falls or cognitive impairment.

The relationship between opioid use and physical activity is complicated by the effects of confounding by indication; opioids are almost always given for pain, and pain is known to be associated with lower objectively measured PA [26]. However, opioids have a wide range of side effects, including cognitive slowing, constipation, and are associated with increased risk of falls – all of which might reduce PA. We did not find an association between opioid use and PA; although participants reporting chronic pain had lower PA levels, opioid use did not significantly interact with pain. Our ability to draw conclusions from that analysis are limited by the small number of participants who were taking opioids. It is interesting to note though that the small number of participants taking opioids who

reported no pain (i.e. their pain was controlled), had non-significantly higher activity counts at baseline than those taking opioids who were still in pain. It is therefore possible that control of pain is more important than opioid use in determining PA levels and future, larger studies could usefully investigate this issue further.

Our analysis has several strengths. We used objective measures of physical activity, which are less prone to recall bias and are better at detecting low PA levels than self-reported measures in older people [27,28]. We measured a wide range of sociodemographic, psychological and environmental factors in our cohort, and linking to routinely collected clinical data enables objective diagnostic information to be used. Similarly, the use of dispensed prescription data avoids recall bias for medication use, and avoids counting prescriptions that were written but never dispensed.

A number of limitations of our analysis require discussion. The statistical power of the analysis was weakened by the relatively small sample size, and by dropouts between baseline and follow up. Differential dropout is likely to have diluted the effects that we observed; participants who declined rapidly are likely to be underrepresented at follow-up as they are more likely to have died or become too unwell or frail to participate. We did not make a distinction between weak and strong opioids, nor between different doses of hypnotics, opioids or anticholinergics. Whilst doing so might have given additional information on dose-response, achieving accurate dose equivalence across different medications is very difficult and likely to introduce error. There are a number of different anticholinergic scores in use; although we chose one that is appropriate to UK prescribing practice, different scales have yielded different strengths of association with outcomes in previous studies [29]. Future analyses could be strengthened both by comparing different anticholinergic scales, by dissecting out the effects of anticholinergics given for different indications (e.g. for overactive bladder, for psychiatric illness, and for other diagnoses) and by examining the cumulative exposure to medications in time-dependent analyses.

There are now a multitude of physical activity monitors commercially available as technology has progressed and a different monitor might more accurately capture physical activity levels in older adults than the RT3 monitor used in this study. Soft tissue motion at the waist has been reported to induce significant errors in belt worn physical activity monitors and it is possible that more modern activity monitors may detect more subtle changes in activity, such as differences in activity patterning or in sedentary time [30]. We did not attempt to convert activity counts to activity levels (e.g. moderate/vigorous or light activity); thresholds for these measures using the RT3 were established in young/middle aged individuals and cannot be considered to be reliable in older people, particularly those with poor physical performance [12]. Whilst this hinders attempts to compare our cohort with other studies, data from other patient groups where RT3 vector magnitude counts have been used reveal that young adults with lower back pain have mean counts approximately twice the level seen in our cohort [31]; older people with heart failure [32] or with functional impairment [33] had mean counts of between 50% and 70% of that seen in our cohort.

Conclusions

We found that anticholinergic burden was associated with greater decline in objectively measured physical activity over time in older people, a finding not seen with hypnotic or opioid use. Given the importance of physical activity levels in older people – both as a factor in developing a range of diseases and as a measure of functional ability – more work is needed to understand the relationship between medication use and activity levels. Understanding these relationships will assist older people and healthcare workers in making optimum choices about medication use so that physical activity is not compromised by treatment of other symptoms or disease states.

Compliance with Ethical Standards

Funding

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Conflicts of Interest

Peter Donnan has received grants from Shire Pharmaceuticals, Gilead Sciences and Novo Nordisk, all outside the submitted work, and is a member of the New Drugs Committee for the Scottish Medicines Consortium. Clare Clarke, Falko Sniehotta, Thenmalar Vadiveloo and Miles Witham declare that they have no conflicts of interest potentially relevant to the content of this study.

Ethical Approval

This study was approved by the Tayside Committee on Medical Research Ethics (09/S1401/57 and 12/ES/0016).

Informed Consent

Written informed consent was obtained from all study participants at baseline and at follow-up.

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Table 1: Baseline details (n=310)

Variable	Mean (SD), Median (IQR) or n (%)
Mean age (yrs) (SD)	77.3 (7.2)
Female sex (%)	169 (54.5)
Median activity count/24hrs (IQR)	141482 (104735)
Comorbid disease from linked data	
Chronic heart failure	9 (2.9)
Myocardial infarction	9 (2.9)
Stroke	5 (1.6)
COPD	5 (1.6)
Diabetes mellitus	25 (8.1)
Cancer (last 5 yrs)	12 (3.9)
Self-reported illness	
Rheumatoid arthritis	21 (6.8)
Osteoarthritis	58 (18.7)
Neurological disease	4 (1.3)
Hypertension	150 (48.4)
Diabetes mellitus	21 (6.8)
Heart disease	95 (30.6)
Cancer	14 (4.5)
Chronic pain	127 (41.0)
Hospital admission in last year	45 (14.5)
Fall in last year	90 (29.0)
Medication use	
Median total number of medications dispensed (IQR)	5 (5)
Median self-reported number of medications (IQR)	3 (5)
Taking opioids (%)	16 (5.2)
Taking hypnotics (%)	21 (6.8)
mARS score mARS 0 (%)	244 (78.6)

mARS 1-2 (%)	37 (12.0)
mARS 3-6 (%)	28 (9.1)
mARS >=7 (%)	1 (0.3)

COPD: Chronic obstructive pulmonary disease. mARS: modified Anticholinergic Risk Scale. SD: Standard deviation. IQR: Interquartile range

Table 2: Unadjusted associations between medication use and baseline activity

Predictor variable		Median count (IQR)	p-value[a]	Change in count per year (95% CI)[b]	p-value
Hypnotics	Non-users	142984 (102507)	0.37	-8844 (-12265, -5423)	0.58
	Users	121789 (104360)		-12522 (-25202, 159)	
Opioids	Non-users	141124 (103936)	0.85	-8498 (-11878, -5118)	0.13
	Users	159888 (107551)		-20006 (-34473, -5539)	
mARS score	0	148181 (108458)	0.14	-7051 (-10729, -3372)	0.03[c]
	1-2	128936 (91458)		-15942 (-25346, -6539)	
	>=3	121482 (99956)		-19544 (-30200, -8887)	

[a]Mann-Whitney U test; Kruskal-Wallis test for mARS score category

[b]General linear model, adjusted for baseline count

[c]p for trend

CI: Confidence interval. IQR: Interquartile range. mARS: modified anticholinergic risk score

Table 3: Adjusted models for medication use vs log of baseline count/24h.

Predictor variable		Model 1			Model 2			Model 3		
		B	95% CI for B	p-value	B	95% CI for B	p-value	B	95% CI for B	p-value
Opioids		0.064	-0.154, 0.283	0.57	0.051	-0.168, 0.270	0.65	0.064	-0.155, 0.283	0.57
Hypnotics		-0.018	-0.209, 0.174	0.86	-0.026	-0.218, 0.165	0.79	-0.034	-0.225, 0.157	0.73
mARS score	0	Referent			Referent			Referent		
	1-2	-0.027	-0.174, 0.120	0.22	-0.037	-0.186, 0.113	0.34	-0.009	-0.162, 0.144	0.53
	>=3	-0.099	-0.265, 0.066		-0.084	-0.257, 0.089		-0.061	-0.237, 0.115	

Model 1: Adjusted for age, sex, deprivation, number of people nearby to turn to, perceived behavioural control, SF-36 physical function

Model 2: As for model 1, with the addition of chronic heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, diabetes mellitus, cancer, hypertension, chronic pain, fall in last year

Model 3: As for model 2, with the addition of total number of other medications taken at baseline

mARS: modified anticholinergic risk score. CI: confidence interval, SF-36: Short Form 36 health questionnaire

Table 4. Adjusted models for medication use vs change in activity (counts/24h) per year of follow up

Predictor variable		Model 1			Model 2			Model 3		
		B	95% CI for B	p-value	B	95% CI for B	p-value	B	95% CI for B	p-value
Opioids		-9037	-22755, 4682	0.20	-6928	-20657, 6801	0.32	-6179	-19779, 7421	0.37
Hypnotics		1666	-10343, 13675	0.79	1167	-10844, 13179	0.85	917	-10956, 12789	0.88
mARS score	0	Referent		0.04†	Referent		0.04†	Referent		0.03†
	1-2	-6781	-16103, 2541		-6529	-15904, 2847		-5847	-15335, 3641	
	>=3	-10333	-21105, 440		-11493	-22330, -656		-11036	-21971, -101	

Model 1: Adjusted for age, sex, deprivation, number of people nearby to turn to, perceived behavioural control, SF-36 physical function and baseline counts/24h

Model 2: As for model 1, with the addition of chronic heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, diabetes mellitus, cancer, hypertension, chronic pain, fall in last year

Model 3: As for model 2, with the addition of total number of other medications taken at baseline

mARS: modified anticholinergic risk score. CI: confidence interval, SF-36: Short Form 36 health questionnaire

†p for trend

Table 5: Interaction between self-reported pain, opioid use and median (IQR) activity counts at baseline

	Opioid use	No opioid use	p-value
Self-reported pain	121789 (94699) (n=11)	135237 (81914) (n=116)	0.67
No self-reported pain	173830 (156977) (n=5)	150283 (119234) (n=174)	0.38
p-value	0.16	0.04	

IQR: Interquartile range