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The effectiveness of a multidisciplinary frailty team in reducing anticholinergic burden in frail older patients: A quantitative service evaluation.

Background:

Increasing evidence suggests drugs known to have anticholinergic properties are an important safety concern in frail older patients and are known to cause cognitive and physical impairment.[1,2,3] Prevalent medications such as antimuscarinics, psychotropic drugs and antihistamines amongst others have been demonstrated to possess anticholinergic activity.[4] These drugs are commonly used for conditions such as urinary incontinence, behavioural and psychological symptoms of dementia and vertigo.

Anticholinergic agents block the neurotransmitter acetylcholine in the peripheral and central nervous systems, resulting in inhibition of parasympathetic nerve impulses causing delirium, constipation, dry mouth and agitation.[5] Although useful in conditions such as those highlighted above, adverse outcomes such as falls, cognitive decline, delirium and increased mortality are frequently overlooked and underestimated by prescribers.[6] Unwanted anticholinergic activity is often referred to as ‘burden’ and interventions to reduce this burden may provide benefit.

Clinicians are taught an awareness of polypharmacy, the risk of drug-drug and drug-disease interactions in older adults however, it is evident that a targeted medicines review to reduce

anticholinergic burden is not currently embedded in routine practice. There are no current national recommendations or standards to assess anticholinergic burden. It relies on an awareness of the concept, the ability to identify those drugs and having the confidence to discontinue offending medicines. Comprehensive Geriatric Assessment (CGA) is an opportunity to address this. CGA is a model of healthcare delivery for frail older patients, triggered once frailty has been identified and is conducted by a specialist team. It is a multifaceted, complex intervention, which aims to inform and modify the decisional algorithm by addressing deviations in medical, psychological, social, functional and environmental well-being. Goal-driven interventions and preventative strategies are then implemented.[6,7] CGA remains the gold standard evidence-based approach for the management of frailty and improves function and quality of life, reduces length of stay and increases the likelihood of both survival and patients remaining in their own home 3-12 months post hospital discharge.[6] CGA is an iterative process which is dependent on the context in which it is put into practice, and is an entry point for a more in-depth analysis, not an end point to stratify interventions as there may be elements of reversibility. It is often misunderstood as an assessment process rather than also encompassing the subsequent case management, health promotion, disease prevention and advanced care planning components, elements that are not often addressed by physicians.

In 2016, a specialist multidisciplinary frailty team (the ‘Frailty Flying Squad’), consisting of Medical Nurse Practitioners, therapists and a consultant geriatrician, was established in the Emergency Department of the Royal United Hospitals Bath NHS Foundation Trust in the United Kingdom. The service was established to address the challenge of increased, unplanned acute frailty admissions, hospital capacity and the need to improve service provision for this complex group of patients. The term ‘frailty’ remains elusive and commonly

misunderstood. With no definitive definitions of frailty, it has been defined as "an ageing-related syndrome of physiological decline, characterised by marked vulnerability to adverse health outcomes".[9] Frail older patients often present with an increased burden of symptoms including weakness and fatigue, medical complexity, and reduced tolerance to medical and surgical interventions.[9] Of people >85 years, 25-50% are living with frailty and only half receive effective health care interventions.[10] The frailty team provides a 7-day service from 8am-8pm providing early identification of frailty and rapid CGA for acutely unwell frail patients.

Identifying anticholinergic burden is part of the targeted medicines review within CGA. The aim of doing so was to improve longer term clinical outcomes, such as reducing cognitive impairment, delirium and risk of falls. Subgroup analysis was conducted to establish whether anticholinergic burden could be reduced in mild, moderate and severely frail patients, as measured by the Rockwood Clinical Frailty Score (CFS).[11] CFS is a cumulative deficit model which stratifies a score based on the severity of cognitive, psychological, social and physical domains of functioning two weeks prior to assessment.[11] Frailty is a dynamic process and a standardised approach to identifying frailty and risk stratification, ensures that modifiable factors and prevention are addressed.[12] Caution needs to be used in the urgent care setting where there is limited evidence for the discriminant validity of frailty scales. Carpenter et al.[13] (2015) highlight that most scales perform better than chance at predicting poor outcomes but none performed adequately for individual clinical decision-making. Until further research is available, clinicians should be mindful that these scales can be used to identify a large population of people who are living with frailty but lack specificity to exclude older people living without frailty.[13]

Eighteen anticholinergic burden tools or scales have been identified.[14] Each differ in how they quantify the anticholinergic activity of medication and clinical outcomes. Adverse outcomes vary between scores resulting in inconsistency of scoring systems as they are validated to capture different elements of drug characteristics and anticholinergic activity. These scales consider anticholinergic burden and poor outcome but few estimate longitudinal exposure, and even fewer have examined cumulative or prolonged exposure. With moderate concordance between the five most frequently used scales, none appear suitable for clinicians for all circumstances.[14]

For the purposes of this study the Anticholinergic Cognitive Burden (ACB) score,[15] was implemented as this tool was more likely to capture medications with modest in vitro antimuscarinic activity affecting physical and cognitive performance.[16] The ACB score is also well-suited for the quantification of ACB exposure and adverse effects in older people[17] and is easy to use. This evidence-based tool does not consider potency or dose but demonstrates, the strongest, most consistent relationship with adverse outcomes such as all-cause hospitalisation for fractures, incidence of dementia and emergency department visits,[18] all of which are preventable or modifiable factors through identification and assessment of frailty. A six-year longitudinal study by Campbell et al.[19] revealed a 46% increase in cognitive impairment within those who were on a drug containing anticholinergic properties. There is a large overlap between frailty and dementia. Dementia contributes to frailty and physical frailty can contribute to cognitive impairment and dementia.[20] It is therefore paramount to identify any contributing factors as there may be an element of reversibility. Comparatively, the ACB tool considered the most regularly used medications, demonstrated the greatest inter-scale agreement and was considered suitable for use in observational studies where anticholinergic burden needs to be quantified.[18] Scales which

measure serum anticholinergic activity could be regarded as more biologically precise however, prospective studies have shown no association between serum anticholinergic burden and cognitive impairment.[17]

The ACB assessment tool is a list of 88 medications based on anticholinergic potency, each medication being awarded a score on a 4-point scale (0=none to 3=very high).[15] The tool measures a person's total exposure to medicines with sedative and anticholinergic properties for all prescribed medicines.[21] A score of 3, found predominantly in urological drugs and antidepressants, carries a particularly high risk of anticholinergic adverse effects and reported associations with delirium.[22] Fox et al.[23] concluded from a 2-year longitudinal study that for each one point increase in ACB score, there was a decline in Mini-Mental State Examination score of 0.33 points. Each 'one point' ACB score increase was also associated with a 26% increase in risk of death and 20% of those taking anticholinergic drugs with a burden score of >4 had died by the end of the study compared to those not taking anticholinergic drugs.[23]

The purpose of the service evaluation reported here was to establish whether the service could successfully reduce anticholinergic burden, using a targeted medicines review, across a range of clinical frailty. Our hypothesis was that there would be a statistically significant reduction in ACB score in patients with mild, moderate and severe frailty, and in the combined patient group.

Method:

Setting, participants and study design

A prospective design was used to collect quantitative data to analyse the effect of targeted medication reviews on ACB scores pre and post medicine review. A subgroup analysis was planned to establish effects in mild, moderate and severely frail groups. The study took place from February 2020 to April 2020 at the Royal United Hospitals Bath NHS Foundation Trust, UK, a 650 bedded District General Hospital for a catchment of around 500,000 people. The population of Bath is older than the national average with 6.2% aged 75 to 84 and 2.7% aged 85 and over.[24]

Prior approval was obtained from the hospital Research & Development team, Caldicott Guardian and the University of West of England Faculty Research Ethics Committee. As the project was classified as a service evaluation, informed consent was not required. Anonymised data was extracted from medical records, with an individual study participant number assigned to each patient. Data extracted included age, sex, CFS and prescribed medications. Only the participant number was recorded in the anonymous study database for the purposes of analysis. A key linking study participant number and medical record number was held separately in an electronic file on a password-protected secure hospital computer for the purposes of data verification.

Sample

A convenience sampling strategy was implemented, which included consecutive patients reviewed by the frailty team who were aged ≥ 75 years, had a CFS of ≥5, and had been admitted with a frailty syndrome (for example, fall, syncope, incontinence, constipation, delirium, dementia or terminal illness). Subgroups were created as follows: CFS 5 = mildly frail 6; = moderately frail; and 7,8 and 9 = severely frail. A CFS score of 7 represents the

beginning of severe frailty through to 9, which represents the terminally ill. Patients who did not fit the above criteria were excluded from data analysis.

Procedure and measures

To ensure prescription records were accurate, a medicines reconciliation was obtained and cross-referenced with information from the patient, carers, electronic General Practitioner records and dosette boxes. Each drug was then individually scored from 1-3 according to Boustani's ACB assessment tool (a score of 0 was assigned if a drug was not on the list). A total score was calculated on admission and immediately recalculated following CGA, which included a targeted medicines review by the frailty team. This involved identifying the indication of each drug and where possible substituting, weaning or stopping offending medicines, without compromising overall therapeutic effectiveness. Changes were made following a shared decision making process with the patient where possible. Piloting of data collection and score calculations were implemented prior to formal data collection by the Medical Nurse Practitioners, to ensure intervention fidelity was maintained between the team members.

Statistical analysis:

The data distributions of each variable were explored using Kolmogorov-Smirnov tests, finding that all but age deviated from a normal distribution. Non-parametric inferential analysis was therefore used throughout using the Wilcoxon signed rank test to investigate changes in ACB scores from before to after medicines review by the frailty team. Data was analysed using IBM SPSS for Mac version 26. Results were considered statistically significant if $p<0.05$.

Results:

129 people (69% female and 31% male) were recruited with a mean ± SD age of 86.6 ± 6.7 years (range 70-101 years). At baseline 59.7% (n=77/129) of patients were prescribed at least one drug with anticholinergic properties which reduced to 48.1% (n=62/129) post review. A Wilcoxon Signed Rank Test was used to determine if there was a statistically significant difference between the pre- and post-review ACB scores. In the total sample, a statistically significant reduction in ACB score was evident from pre- to post-review (p=0.001, mean score reduced from 1.04 to 0.77) (Table 1).

Of those with an ACB score of 1, a reduction to zero was achieved in 27.5% (n=14/51). Of those scoring 2-3, a reduction to zero was achieved in 20.0% (n=4/20). A reduction from a clinically significant score of 3 or above to 2 or below was possible in 40.0% (n=6/15). It was noted that 2.3% (n=3/129) of ACB naive patients were started on an anticholinergic drug (i.e. ACB score 0 pre- to 1 post-review) but there were no other examples of patients experiencing an increase in ACB score during their admission.

Subgroup analysis was divided into the following categories. Mild (CFS 5) 28.7% (n=37/129), moderate (CFS 6) 50.4% (n=65/129) and severe (CFS 7, 8 and 9) 20.9% (n=27/129). There was a statistically significant reduction in ACB scores in the mild (p=0.013) and moderate (p=0.003), and borderline non-statistical significance in the severe category (p=0.066). 28 out of 88 anticholinergic drugs were identified, most commonly diuretics, antipsychotics, beta-blockers, anticoagulants, anti-muscarinics, opioids and H_2 antagonists. During this study, anecdotal factors such as time, clinician preference, a reluctance to switch drug classes and fear of negative consequences were observed by the

team members. Themes such as these and a lack of awareness outside of specialist teams may explain why DB_{AC} prescribing trends have remained the same over the last decade.[25]

Discussion:

This study demonstrated a statistically significant reduction in overall ACB score post medications review by the frailty team, confirming that it is possible to reduce DB_{AC} in frail older adults during acute unplanned admissions in the Emergency Department. 59.7% (n=77/129) of patients were identified as using at least one drug containing anticholinergic properties and this is consistent with other studies using the ACB assessment tool.[26, 27, 28] Subgroup analysis of mild, moderate and severely frail categories, revealed a statistically significant reduction in the mild and moderately frail categories and a borderline non statistically significant result in the severely frail category. To our knowledge this has not previously been examined in other studies.

Direct comparison between other studies analysing DB_{AC} reduction is challenging due to the abundance of scales developed to assess DB_{AC}. This makes interpretation of data difficult as they are validated to capture different elements of drug characteristics, for instance central versus peripheral anticholinergic effects. Despite this, all anticholinergic scales support the hypothesis that anticholinergic drugs have a negative impact and that increased age potentially goes hand-in-hand with risk of multi-morbidity and polypharmacy[10]

Drugs containing anticholinergic properties are associated with frailty[28] and are a plausible cause of cognitive impairment.[29] Risacher *et al's*[30] (2016) 2-year longitudinal study echoed this, demonstrating that anticholinergic drug use increased brain atrophy and dysfunction clearly evident on neuroimaging and cognitive testing. Richardson *et al*.[22] (2018) agree that

there were robust associations with anticholinergic use and dementia 20 years after exposure. In contrast, Kersten *et al*.[31] (2013) questioned the reversibility of anticholinergic cognitive effects. It may be argued that there is finite time to benefit from potential reversibility in severe frailty, as there may be limited life expectancy and reversibility may depend on an individual's pathological cholinergic dysfunction. It is evident that more longitudinal studies are required with pre-frail rather than moderately and severely frail patients in order to establish the clinical significance of reducing DB_{AC}.

On the contrary, anticholinergic scores highlight an association with cumulative effects of these drugs and an increased cognitive impairment with a dose-response relationship.[32] It is these potent drugs that are significantly associated with increased mortality[33] and potentially a transition between robust state to prefrail.[34] However, there has only been one longitudinal study conducted correlating frailty state and the use of at least one potentially inappropriate medication, finding in a small increased risk of becoming frail.[35] Large randomised trials and observational studies provide insight however, they are highly heterogenous[1,36,37] -due to variation in underlying disease processes, individual responses and prognoses. This heterogeneity, makes it difficult to determine exactly what may cause a transition in cognitive or physical frailty or the amount of ACB reduction required to improve clinical outcomes. However, there is consensus that anticholinergic drugs cause loss of functionality.[8,18]

The current study supports existing evidence that anticholinergic drug use is prolific with multiple studies highlighting up to 87% of frail older people taking at least one medication containing anticholinergic properties, despite known adverse side effects and the risk profile.[26,27,38] Wide variation in prescribing practice is evident. For instance, a large multi-

centre study based in the UK and Europe[28] revealed a similar proportion of patients were admitted on anticholinergic drugs (60.8% versus 59.7% in our study) but they had a higher mean ACB score (2.1±1.5 range 1-10, versus 1.04±1.35 range 1-7 and a higher number of anticholinergic drugs 56 versus 28). It was noted that patients in the United Kingdom and Finland, were unlikely to have their baseline ACB score increased which highlights geographical variation in prescribing trends. An awareness of the obstacles that impede the efforts to reduce anticholinergic drug use is paramount.

A small proportion of patients were commenced on an anticholinergic drug temporarily during their admission, mirroring findings by Collamati *et al.*[8], 2016 and Weichert[28], 2018. These drugs were predominantly diuretics such as intravenous furosemide, prednisolone and codeine, in response to conditions such as decompensated congestive cardiac failure (CCF), exacerbation of COPD and fractures as a result of a fall. This temporary increase was reflected in their post-review score, which may or may not have continued long term. Where possible a non-anticholinergic therapeutic alternative was considered, for instance bisoprolol over digoxin or bumetanide rather than furosemide. However, if intravenous diuretics were required due to the severity of CCF, intravenous furosemide was considered the only option which carried an individual ACB score of 1. These drugs carry low individual DB_{AC} and cannot always be avoided. A post score review on discharge may have indicated a further reduction in ACB score.

This study demonstrates that, with 59.7% of patients being admitted on at least one anticholinergic drug there is a need for increased anticholinergic awareness and improved prescribing. However, priority should always be given to clinical need remembering that in some instances drugs may exert compensatory protective effects on cognitive dysfunction

despite their low individual anticholinergic load (for example selective cardiovascular drugs).[22] Drugs aimed at enhancing quality of life, such as antimuscarinics for urinary incontinence that carry high DB_{AC} should not routinely be discontinued if there is clinical benefit although the reporting of quality of life data in frailty to support this is scarce and contradictory.[39] Prescribing practices driven by economic convenience or reflex should be discouraged and an anticholinergic drug should only be prescribed with informed consent and regular review when all other avenues such as bladder training and alternative methods have been exhausted.

Whilst every effort should be focused on discontinuation and reduction of DB_{AC} it is worth remembering that abrupt discontinuation should be avoided due to risk of cholinergic rebound for instance: agitation; vomiting; diarrhoea and tachycardia.[40] Particular caution is needed with antipsychotic drugs which are particularly challenging due to the risk of extrapyramidal symptoms with both their long-term use and abrupt withdrawal. Patients admitted on antidepressants and antipsychotics were a common observation. Weaning doses were possible in some instances however, not detected in the post review results, as tapering doses were not reflected in the ACB tool. Despite this, a partial reduction may still provide longer-term cognitive benefits as illustrated by Fox *et al*.[23] Other patients would require older age psychiatry input to consider whether weaning of antipsychotic drugs was feasible.

Frailty is a dynamic process often misconceived as untreatable. Early identification, prevention and intervention can maintain independence, slow decline and ultimately prevent people reaching crisis point. With the introduction of the electronic frailty index in the UK, a key component of the general medical services contract,[41] routine identification and

management of frailty should be simplified. Information technology is capable of identifying patients on high-risk medicines however, in the first instance, education programs highlighting the dangers of prescribing anticholinergic drugs in Primary Care are required as it is clear from this study that a significant proportion of patients are still being prescribed these drugs. The National Institute for Health and Care Excellence could consider revising their 'Dementia, disability and frailty approach to delay or prevent onset overview'[42] clinical pathway to incorporate a (prefrail) midlife-targeted medication review, in order to negate unnecessary DB_{AC} and potential future cognitive impairment.

Prescribing for frail elderly patients is complex and a targeted medicines review can be viewed as time consuming requiring extensive communication, monitoring and follow up. Despite this, the current study highlights that a frailty multidisciplinary team are well placed in the Emergency Department and capable of undertaking this. There is a need to focus on outcomes relevant to the patient and to weigh up complex decisions based on risk versus benefit although it is unclear whether it would be safe to conduct this in a non-specialist setting. Understanding obstacles and factors that influence efforts to reduce DB_{AC} are pivotal. Lack of standardisation and guidance quantifying anticholinergic scoring and the amount of reduction required to improve clinically significant outcomes remains unclear. Despite this, the body of evidence suggests that anticholinergic drugs facilitate neurotransmitter down regulation.[43] Reduced anticholinergic cognitive burden may result in improved short-term memory and future longitudinal studies would be warranted to investigate further the 'number needed to treat' to establish the effectiveness of this intervention and identify whether targeting individual patients versus the general population achieves improved clinically significant outcomes. Further still, exploration of the relationship between withdrawal of anticholinergic drug exposure and cognitive and frailty transitions

would be beneficial as both non-pharmacological and pharmacological therapies to treat frailty remain elusive. Efficacy and reverse causation should be at the forefront of a medication review balancing under treatment and over treatment for this complex group of patients where disease modification and prevention becomes less meaningful in frail people.

Limitations:

This study was conducted at a single centre using convenience sampling to accommodate shift patterns and a limited timeframe. This resulted in difficulty ensuring equal proportions of patients in frailty subgroups. A smaller sample of severely frail patients was expected due to robust advance care planning and admission avoidance however, this may have impacted on statistical significance for this subgroup due to the sample being underpowered. In conjunction, these patients would most likely have had recent or even multiple admissions whereby a targeted medication review had already occurred. A small team of Medical Nurse Practitioners and Geriatricians conducting a service evaluation on their own team could potentially introduce an element of bias. Potential variation in prescribing practices means that it may not be reproducible, generalisable or sustainable. In future, having a clinical pharmacist on the team would give added confidence regarding tapering of medications, monitoring advice and ensuring continuity of prescribing practices.

This small study included acute short-term medications such as prednisolone and furosemide which would have elevated the post review score temporarily. Likewise, weaning doses were not reflected due to the scale used. A dose weighted scale, recalculation of ACB score on discharge or a month post discharge may have revealed an even higher reduction in ACB score. We were unable to conduct patient follow up to assess for adverse reactions

or withdrawal symptoms related to deprescribing due to time and resources nor obtain evidence for improved clinical outcomes.

Conclusion:

This study has shown that a specialist multidisciplinary team based in the Emergency Department are well placed to perform targeted medication reviews and can significantly reduce anticholinergic drug exposure in frail older patients as measured by the ACB scale. It is evident from this study that patients are still prescribed drugs of questionable benefit in relation to limited life expectancy and near end of life. It is unknown to what extent anticholinergic exposure contributes to the transitions between cognitive and physical frailty stages and subsequent progression to death however, this study highlights that there are opportunities to negate harm. Frailty is not an inevitable part of ageing, therefore clinicians must remain vigilant when instigating new treatments and consider alternatives where possible in order to mitigate harm and the progression of frailty. Deprescribing in the frail is complex and challenging, should remain patient focused and be based on the most recent clinical evidence alongside clinical judgment. A paradigm shift in prescribing practice is urgently required to reduce variation, and to provide effective and sustainable healthcare for frail older patients.

Table 1. Demographics and ACB scores pre-post review in the total cohort (n=129) and each clinical frailty sub-group.

	CFS 'Mild' (CFS=5) n=37	CFS 'Moderate' (CFS=6) n=65	CFS 'Severe' (CFS=7-9) n=27	Total (CFS=5-9) n=129
Age, mean± SD	86.41 ± 6.47	86.32 ± 6.51	87.70 ± 7.68	86.64 ± 6.73

Sex, Women:Men	28:9	43:22	18:9	89:40
CFS, mean ± SD	5.00 ± 0.00	6.00 ± 0.00	7.19 ± 0.11	5.96 ± 0.07
ACB score Pre, mean ± SD	1.27 ± 1.47	1.03 ± 1.39	0.74 ± 1.02	1.04 ± 1.35
ACB score Post, mean ± SD	0.89 ± 0.99	0.82 ± 1.36	0.48 ± 0.85	0.77 ± 1.17
Change in ACB score Pre-Post (p-value, Wilcoxon test)	p=0.013*	p=0.003*	p=0.066	p=0.001*

***Statistically significant (p<0.05). ACB=Anticholinergic Cognitive Burden score, CFS=Clinical Frailty Score, n=Number, SD=Standard Deviation.**

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