Anticholinergic medicines in an older primary care population: a cross-sectional analysis of medicines’ levels of anticholinergic activity and clinical indications

P. J. Magin* PhD FRACGP, S. Morgan† MPH & TM FRACGP, A. Tapley‡ MMedStat, C. McCowan§ PhD, L. Parkinson¶ PhD, K. M. Henderson‖ B Nurses, C. Muth** MD MPH, M. S. Hammer*** MSc, D. Pond* PhD FRACGP, K. E. Mate†† PhD, N. A. Spike‡‡ MBBS FRACGP, L. A. McArthur§§ MBBS FRACGP FACRRM and M. L. van Driel¶¶ PhD FRACGP

*School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, †Elmore Vale General Practice, Newcastle, NSW, ‡GP Synergy, Newcastle, NSW, Australia, §University of Glasgow, Glasgow, UK, ¶School of Human Health and Social Sciences, Central Queensland University, Rockhampton, QLD, Australia, **Institute of General Practice, Johann Wolfgang Goethe University, Frankfurt am Main, Germany, ††School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW, ‡‡Eastern Victoria GP Training, Melbourne, VIC, §§University of Adelaide, Adelaide, SA, and ¶¶School of Medicine, University of Queensland, Brisbane, QLD, Australia

Received 16 March 2016, Accepted 2 June 2016

Keywords: anticholinergic agents, elderly, general practitioner, primary care

SUMMARY
What is known and objectives: Adverse clinical outcomes have been associated with cumulative anticholinergic burden (to which low-potency as well as high-potency anticholinergic medicines contribute). The clinical indications for which anticholinergic medicines are prescribed (and thus the ‘phenotype’ of patients with anticholinergic burden) have not been established. We sought to establish the overall prevalence of prescribing of anticholinergic medicines, the prevalence of prescribing of low-, medium- and high-potency anticholinergic medicines, and the clinical indications for which the medicines were prescribed in an older primary care population.

Methods: This was a cross-sectional analysis of a cohort study of Australian early-career general practitioners’ (GPs’) clinical consultations – the Registrar Clinical Encounters in Training (ReCEnT) study. In ReCEnT, GPs collect detailed data (including medicines prescribed and their clinical indication) for 60 consecutive patients, on up to three occasions 6 months apart. Anticholinergic medicines were categorized as levels 1 (low-potency) to 3 (high-potency) using the Anticholinergic Drug Scale (ADS). Results: During 2010–2014, 879 early-career GPs (across five of Australia’s six states) conducted 20 555 consultations with patients aged 65 years or older, representing 35 506 problems/diagnoses. Anticholinergic medicines were prescribed in 10.4% [95% CIs 9.5–10.5%] of consultations. Of the total anticholinergic load of prescribed medicines (‘community anticholinergic load’) 72.7% [95% CIs 71.0–74.3%] was contributed by Level 1 medicines, 0.8% [95% CIs 0.5–1.1%] by Level 2 medicines and 26.5% [95% CIs 24.8–28.1%] by Level 3 medicines. Cardiac (40.0%), Musculoskeletal (16.9%) and Respiratory (10.6%) were the most common indications associated with Level 1 anticholinergic prescription. For Level 2 and 3 medicines (combined data), Psychological (16.1%), Neurological (16.1%), Musculoskeletal (15.7%) and Urological (11.1%) indications were most common.

What is new and conclusion: Anticholinergic medicines are frequently prescribed in Australian general practice, and the majority of the ‘community’ anticholinergic burden is contributed by ‘low’-anticholinergic potency medicines whose anticholinergic effects may be largely ‘invisible’ to prescribing GPs. Furthermore, the clinical ‘phenotype’ of the patient with high anticholinergic burden may be very different to common stereotypes (patients with urological, psychological or neurological problems), potentially making recognition of risk of anticholinergic adverse effects additionally problematic for GPs.

WHAT IS KNOWN AND OBJECTIVES
Many older patients use medicines with anticholinergic properties. In a recent Australian study, 42% of people over 75 years were taking at least one anticholinergic medicine. That is, they were using a medicine with acetylcholine receptor antagonist activity. The degree of anticholinergic effect varies greatly between medicine classes and varies between individual medicines within those classes. Classes of medicines traditionally recognized as being associated with anticholinergic effect include gastrointestinal antisipasmodics, medicines used for urinary urge incontinence, antipsychotics, tricyclic antidepressants (which are often used in older patients for non-psychiatric indications, including pain modulation), anti-Parkinsonian medicines and antihistamines. These medicines are often grouped as potentially inappropriate for use in the elderly due to their strong anticholinergic effects.

The anticholinergic effect of a medicine may be intrinsic to the intended effect (such as the effect on cholinergic receptors in bladder overactivity) or may be an unintended effect. Anticholinergic effects of medicines in a patient’s medicines regimen may be additive, constituting anticholinergic ‘burden’ or ‘load’. Anticholinergic burden has been associated with cognitive impairment, confusion, falls, hospital admission and duration of admission, impairment in activities of daily living, poorer quality of life, depression, incident cardiovascular disease and mortality.

We have previously conducted two studies of the use of anticholinergic medicines by older Australians: a retrospective analysis of prescribing records linked to survey data from a community-based female cohort; and an analysis of the medicines regimens of patients at baseline in a trial of peer education of general practitioners (GPs). The first of these studies linked participants in the cohort study to national prescribing data. The...
second involved direct observation and recording of each participant’s medicines by nurses visiting participants’ homes. In both studies, individual patient anticholinergic burden was driven more by multiple low-potency anticholinergic medicines than by medicines of high anticholinergic potency that clinicians would traditionally be aware of as being ‘anticholinergic’.1,13 Anticholinergic burden may thus be at least partially ‘invisible’ to clinicians treating older patients. The characteristics of these ‘invisible’ medicines and the context of their prescription are thus of clinical importance. In neither of these studies (as in most research in this area) was linkage of anticholinergic medicines to indication for their prescription possible.

In this study, we present a secondary analysis of data from a study of early-career GPs’ clinical practice (including prescribing). We sought to document the frequency of individual anticholinergic medicines’ prescription (both high and low potency) for older patients and the problems/diagnoses for which the anticholinergic medicines were prescribed. We did not aim to calculate individual patients’ anticholinergic burden.

METHODS
This was a cross-sectional analysis of data from the Registrar Clinical Encounters in Training (ReCEnT) cohort study. The detailed study methodology has been described elsewhere.20 Briefly, ReCEnT is an ongoing cohort study of the in-consultation clinical practice of doctors at the beginning of their careers in primary care – general practice registrars (trainees) enrolled with five of Australia’s 17 general practice regional training providers (RTPs). Geographically, the five RTPs encompass urban, rural, remote and very remote practices in five of Australia’s six states. All registrars in participating RTPs complete data collection as part of their educational programme and may choose to consent to their data being also used for research purposes.

Registrars spend at least three–6-month full-time-equivalent terms in general practice settings. This is the compulsory general practice component of their 3-year training programme. During this general practice component, registrars effectively operate as independent practitioners, although having recourse to the advice and assistance of experienced clinical supervisors. This independence includes prescribing authority (and capacity to order and supply of medicines (although whether it was prescription, over-the-counter (OTC) non-prescription medicines and direct supply of medicines (although whether it was prescription, recommendation or supply was not recorded). Medicines were coded via the Anatomical Therapeutic Chemical (ATC) classification system, and medicines with anticholinergic effects were identified using the Anticholinergic Drug Scale (ADS)21 updated to reflect current Australian medicines availabilities (informed by AMH Australian Medicines Handbook,19 and a recent review18). The ADS categorizes medicines in an ordinal fashion from 0 to 3 (0: ‘no known anticholinergic properties’; 1: ‘potentially anticholinergic as evidenced by receptor binding studies’; 2: anticholinergic adverse events sometimes noted, usually at excessive doses; and 3: markedly anticholinergic).21 Scores on the ADS predict clinical outcomes associated with anticholinergic effects2 and the ADS performs well in this regard compared to other anticholinergic scales.7 We did not adjust our scoring for drug dose. This has not been shown to provide significantly different results to simple scoring when evaluating association of anticholinergic burden with serum anticholinergic activity21 and with clinical parameters.1

The ADS is usually used to create summary estimates of individual patient anticholinergic burden. We did not have data on individual patients’ complete medicines regimens, only data of which medicines were prescribed at that consultation. The focus of this study, then, was to examine overall prescribing of anticholinergic medicines and the conditions for which they are prescribed. This could be seen to represent ‘community’ rather than ‘individual’ anticholinergic burden.

Independent variables
Problems managed or diagnoses made during the consultation were coded according to the International Classification of Primary Care, Second Edition classification system (ICPC-2).22 Individual diseases/problems are categorized in ICPC-2 to seventeen systems-based chapters (cardiovascular, neurological, psychological, urological, etc.).

Analyses
Analyses were undertaken only for patients aged 65 years and older.

We calculated proportions of all prescribed medicines that were rated as 1, 2 or 3 by the ADS. Estimates included 95% confidence intervals, adjusted for clustering of patients within registrar. Similarly, we calculated the proportion of all consultations and the proportion of all problems/diagnoses within this patient group that resulted in prescription of an ADS-defined anticholinergic medicine.

We then calculated the proportion of the overall cumulative ADS-scored anticholinergic burden of the medicines prescribed by all registrars during their collection periods (‘community anticholinergic burden’) that was due to Level 1, 2 or 3 medicines.

We also identified the most commonly prescribed medicines in each ADS level, the most common problems/diagnoses for which medicines of each ADS level were prescribed, and the proportions of medicines from each ADS level by ICPC-2 disease chapter. For the problem/diagnoses for which anticholinergic medicines were prescribed (in each ADS level), ICPC-2 codes describing clinically equivalent diagnoses were collapsed to single descriptive categories by a clinician member of the research team.

Analyses were programmed with STATA 11.2. (Statacorp, College Station, TX, USA)
Anticholinergic medicines were prescribed in 10.4% [95% CIs 9.8–11.0%] of consultations, for 6.2% [95% CIs 5.9–6.6%] of problems/diagnoses managed (see Table 2).

Using ADS scoring of medicines prescribed, of the total prescribed anticholinergic burden (‘community’ anticholinergic burden) 72.7% [95% CIs 71.0–74.3%] was contributed by Level 1 medicines, 0.8% [95% CIs 0.5–1.3%] by Level 2 medicines and 26.5% [95% CIs 24.8–28.1%] by Level 3 medicines (Table 2).

The most commonly prescribed anticholinergic medicines, by ADS level, are presented in Table 3, and the most common indications (diagnoses or problems) for which they are prescribed are presented in Table 4.

There was marked variation by ADS level in the ICPC-2 disease chapters for which the anticholinergic medicines were prescribed. For Level 1 medicines, Cardiac (40.0% [95% CI: 36.9–43.2%]), Musculoskeletal (16.9% [95% CI: 15.0–18.9%]) and Respiratory (10.6% [95% CI: 9.2–12.1%]) were the most common ICPC-2 chapters associated with anticholinergic prescription. For Level 2 and 3 medicines (combined data), Psychological (16.1% [95% CI: 12.9–21.2%]), Neurological (16.1% [95% CI: 9.2–17.1%]), Musculoskeletal (15.7% [95% CI: 11.3–21.4%]) and Urological (11.1% [95% CI: 7.8–15.5%]) were the most common ICPC-2 chapters associated with anticholinergic prescription. The relative contributions of all ICPC-2 chapter groupings of problems/diagnoses to each ADS-level prescription are presented in Fig. 1.

WHAT IS NEW AND CONCLUSION

Principal findings and comparison with previous literature

We have demonstrated that the prescription of medicines with anticholinergic properties by Australian GP registrars is common in older patients (10.0% of all medicines and in 10.4% of consultations) and that anticholinergic burden is driven mainly by less potent anticholinergic medicines. This is consistent with previous Australian research examining the issue of anticholinergic use with differing methodological approaches.19 We found that 72.7% of overall ‘community’ anticholinergic burden was due to ADS Level 1 medicines. In another Australian study, the contribution of ADS Level 1 medicines to ‘individual’ anticholinergic burden was 70.5% in patients without dementia and 64.5% in those with dementia.

A singular clinical circumstance where surveillance for possible anticholinergic medicines should be especially rigorous is that of utilization of anticholinergic drugs in patients with dementia treated with cholinesterase inhibitors. In an Australian study of this circumstance,20 a majority of anticholinergic medications used concurrently with cholinesterase inhibitors were Level 1 medicines.

We found a broad spectrum of indications for the use of medicines with anticholinergic properties, and that this spectrum differs by the level of anticholinergic potency of the individual medicine (as presented in Table 3). The pervasiveness of the use of medicines with low-potency anticholinergic properties across a broad range of indications means that cumulative burden may be relatively ‘invisible’ to the treating clinician.

Our findings regarding the prescription of individual anticholinergic medicines can be compared with that of previous studies. Whereas there are broad commonalities, it is striking that the most commonly prescribed medicine with anticholinergic properties in our study was warfarin. Warfarin was a commonly prescribed anticholinergic medicine in previous Australian
Table 2. Anticholinergic medicines by Anticholinergic Drug Scale level – number prescribed; number of problems prescribed for; number of consultations prescribed during; and contribution to ‘anticholinergic burden’

<table>
<thead>
<tr>
<th>Anticholinergics</th>
<th>Medications (n = 23 308)</th>
<th>Problems* (n = 35 506)</th>
<th>Consultations* (n = 20 555)</th>
<th>‘Anticholinergic burden’ contribution (%) [95% CIs]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) [95% CIs]</td>
<td>n (%) [95% CIs]</td>
<td>n (%) [95% CIs]</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2323 (10.0) [9.5–10.5]</td>
<td>2208 (6.2) [5.9–6.6]</td>
<td>2136 (10.4) [9.8–11.0]</td>
<td>2835 (100)</td>
</tr>
<tr>
<td>Level 1</td>
<td>2061 (8.8) [8.4–9.3]</td>
<td>1968 (5.5) [5.2–5.9]</td>
<td>1904 (9.3) [8.7–9.8]</td>
<td>2061 (72.7) [71.0–74.3]</td>
</tr>
<tr>
<td>Level 2</td>
<td>12 (0.05) [0.03–0.09]</td>
<td>12 (0.03) [0.02–0.06]</td>
<td>12 (0.06) [0.03–0.1]</td>
<td>24 (0.8) [0.5–1.3]</td>
</tr>
<tr>
<td>Level 3</td>
<td>250 (1.1) [0.9–1.2]</td>
<td>249 (0.7) [0.6–0.8]</td>
<td>247 (1.2) [1.1–1.4]</td>
<td>750 (26.5) [24.8–28.1]</td>
</tr>
</tbody>
</table>

CI, confidence interval.
*An individual problem or consultation could be associated with prescription of more than one anticholinergic medicine.

Table 3. Most common individual medicines prescribed from each Anticholinergic Drug Scale level

<table>
<thead>
<tr>
<th>Anticholinergic Drug Scale level</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>539 (26.15)</td>
<td>8 (66.67)</td>
<td>136 (54.40)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>332 (16.11)</td>
<td>2 (16.67)</td>
<td>32 (12.80)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>288 (13.97)</td>
<td>2 (16.67)</td>
<td>23 (9.20)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>288 (13.97)</td>
<td>2 (16.67)</td>
<td>11 (4.40)</td>
</tr>
<tr>
<td>Procyclidine</td>
<td>128 (6.21)</td>
<td>2 (16.67)</td>
<td>10 (4.00)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>77 (3.74)</td>
<td>2 (16.67)</td>
<td>7 (2.80)</td>
</tr>
<tr>
<td>codeine</td>
<td>69 (3.35)</td>
<td>2 (16.67)</td>
<td>6 (2.40)</td>
</tr>
<tr>
<td>Oxycodone, combinations</td>
<td>67 (3.25)</td>
<td>2 (16.67)</td>
<td>6 (2.40)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>58 (2.81)</td>
<td>2 (16.67)</td>
<td>5 (2.00)</td>
</tr>
<tr>
<td>Morphine</td>
<td>56 (2.72)</td>
<td>2 (16.67)</td>
<td>2 (0.80)</td>
</tr>
</tbody>
</table>

Table 4. Individual indications (problems or diagnoses*) for which each level of anticholinergic medicines was prescribed: most common indications

<table>
<thead>
<tr>
<th>Level 1 medicines</th>
<th>n (%)</th>
<th>Level 2 medicines</th>
<th>n (%)</th>
<th>Level 3 medicines</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>219 (11.1)</td>
<td>Epilepsy</td>
<td>2 (16.7)</td>
<td>Bladder instability/incontinence/nocturia</td>
<td>29 (11.7)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>219 (11.1)</td>
<td>Allergic reaction</td>
<td>1 (8.3)</td>
<td>Neuropathic pain</td>
<td>25 (10.1)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>140 (7.1)</td>
<td>Migraine</td>
<td>1 (8.3)</td>
<td>Pain (other than back or neuropathic pain)</td>
<td>20 (8.1)</td>
</tr>
<tr>
<td>Pain (other than back pain)</td>
<td>140 (7.1)</td>
<td>Peripheral neuropathy</td>
<td>1 (8.3)</td>
<td>Depression</td>
<td>19 (7.7)</td>
</tr>
<tr>
<td>Back pain/SCIatica</td>
<td>111 (5.6)</td>
<td>Chronic pancreatitis</td>
<td>1 (8.3)</td>
<td>Back pain/SCIatica</td>
<td>17 (6.9)</td>
</tr>
<tr>
<td>Vertigo dizzy</td>
<td>87 (4.4)</td>
<td>Lumbar spinal stenosis</td>
<td>1 (8.3)</td>
<td>Dermatitis/eczema</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary</td>
<td>86 (4.4)</td>
<td>Trigeminal neuralgia</td>
<td>1 (8.3)</td>
<td>Headache/migraine</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Disease Arthritis (including gout)</td>
<td>69 (3.5)</td>
<td>Pruritus</td>
<td>1 (8.3)</td>
<td></td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Other than osteoarthritis</td>
<td>63 (3.2)</td>
<td>Anxiety</td>
<td>1 (8.3)</td>
<td></td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 (2.9)</td>
<td>Osteoarthritis</td>
<td>1 (8.3)</td>
<td></td>
<td>4 (1.6)</td>
</tr>
</tbody>
</table>

*Prescriptions’/‘renewal of medication’ not presented.

studies,1,19 but not in international studies,7 using the ADS. The comparison will not reflect differences in use of novel oral anticoagulant medicines as the studies predate their widespread use. The finding may represent relatively aggressive anticoagulant management in older patients in Australia, especially for atrial fibrillation, reflecting national policy.24 This finding is unlikely to affect the generalizability to other countries of our conclusions regarding the prominence of cardiovascular medicines among anticholinergic medicines as this would persist even with more modest levels of warfarin usage. Also of note was the frequency of prescription of oxycodone in our findings. Oxycodone was among the 10 most commonly used anticholinergic medicines in subjects with high ADS scores in an Australian study,19 but was not in the most common ADS-rated anticholinergic medicines elsewhere.
Although codeine was, this may reflect recent alarmingly steep increases in rates of oxycodone prescribing in Australia, especially to patients aged over 70 years.

Strengths and limitations

The study has a number of strengths. The response rate is very high for a study of GPs, allowing confidence that we have accurately captured prescription patterns. The major strength is that unlike many studies of anticholinergic medicines, we have close linkage of prescribed medicine to its indication. We also have, unusually in studies of anticholinergic medicines, ascertainment of recommended and physician-supplied as well as prescribed medicines. This is particularly important as several strongly anticholinergic medicines (antihistamines) are over-the-counter medicines which do not require a doctor’s prescription in Australia.

The major limitation is that our study elicits ‘snapshot’ data of consultation content, and we do not collect patients’ full medicines regimens. Thus, our estimations of individual medicines’ contributions to anticholinergic load are at the population rather than individual patient level, and do not document clustering of anticholinergic medicines within individuals. A further limitation, common to studies in this area, is that in vivo anticholinergic effects of medications are inherently difficult to quantify (as is apparent from the many currently used measures of anticholinergic medicines effects) and the updates to the validated ADS that we used in this analysis have not been validated.

Whereas the generalizability to Australian practice is strong (participation by five of Australia’s 17 RTPs across five of Australia’s six states and encompassing urban, rural, remote and very remote practices), generalizability to those countries with differing health and GP training systems is uncertain.

Implications for practice and future research

Our study demonstrates the high volume of prescription of medicines with anticholinergic effects in general practice – 10% of all prescriptions to those 65 years and over. Thus, adverse effects attributable to anticholinergic burden are potentially a major health issue.

It has been for some time accepted that the propensity to be prescribed highly anticholinergic medications for conditions such as urinary incontinence and chronic neuropathic pain may predispose older patients to high anticholinergic burden. Our study suggests that this known propensity of older patients to anticholinergic adverse effects is further heightened by previously invisible low-level anticholinergic medicines, especially medicines for cardiovascular and musculoskeletal morbidities. Further, the clinical ‘phenotype’ of the older patient with high anticholinergic burden may often not conform to the ‘traditional’ phenotype of a patient with urinary incontinence or urgency, neuropathic pain or psychiatric illness. This traditional phenotype is exemplified by a study of anticholinergic medicines pre- and post-hospital admission which ignored Level 1 anticholinergics and considered only Level 2 and 3 anticholinergic medicines. The authors concluded that ‘groups of patients [can be] recognised to whom special attention should be paid regarding possible anticholinergic effects of prescribed drugs’ and that these groups were patients with ‘urinary incontinence and retention, constipation, gastroduodenal ulcer disease as well as neurologic and psychiatric comorbidities’. Although we have not measured individual patient anticholinergic burden, our findings of overall levels and patterns of anticholinergic medicines prescription suggest that many older patients with high anticholinergic burden may have considerable anticholinergic contributions from medicines for cardiac disease or...
Anticholinergic medicines are frequently prescribed in Australian general practice, and the majority of the ‘community’ anticholinergic burden is contributed by ‘low’-anticholinergic potency medicines. GPs will need education and assistance to appreciate the importance of these ‘invisible’ anticholinergic medicines (and the patient contexts in which they are prescribed, including patient ‘phenotype’) and to incorporate calculations of individual patient anticholinergic burden into their clinical decision-making. This has the potential to limit patients’ anticholinergic burdens and thus reduce the potential for adverse drug effects.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the GP registrars, GP supervisors and practices who have participated in the ReCEnT project.

FUNDING

There was no external funding. The funding of the project was by the participating Regional Training Providers, which are funded by the Australian Commonwealth Government.

CONFLICT OF INTEREST

All authors declare no conflict of interests.

REFERENCES

Anticholinergic medicines in a primary care population

P. J. Magin et al.


