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Authors

1. Parker J. Magin
2. Simon Morgan
3. Amanda Tapley
4. Colin McCowan
5. Lynne Parkinson
6. Kim M. Henderson
7. Christiane Muth
8. Marc Stefan Hammer
9. Dimity Pond
10. Karen E. Mate
11. Neil A. Spike
12. Lawrie A. McArthur
13. Mieke L. van Driel

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Corresponding author

Professor Parker Magin

School of Medicine and Public Health, University of Newcastle, University Drive, Callaghan
2308, NSW, Australia

parker.magin@newcastle.edu.au

phone: +61 408953872

fax: +61 2 49686733

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Conflicts of interest

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Abstract

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) has not been established. We sought to establish the overall prevalence of anticholinergic medicines prescribing, the prevalence of low-, medium- and high-potency anticholinergic medicines prescribing, and the clinical indications for which the medicines were prescribed in an older primary care population.

Methods

A cross-sectional analysis of a cohort study of Australian early-career general practitioners' (GPs') clinical consultations – the Registrars 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 six months apart. Anticholinergic medicines were categorised as Levels 1 (low-potency) to 3 (high-potency) using the Anticholinergic Drug Scale (ADS).

Results

During 2010-14, 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 0.5-1.3] 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 Levels 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.¹ That is, they were using a medicine with acetylcholine receptor antagonist activity.^{2,3} The degree of anticholinergic effect varies greatly between medicine classes and varies between individual medicines within those classes.³ Classes of medicines traditionally recognised as being associated with anticholinergic effect include gastrointestinal antispasmodics, 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.²⁻⁵ These medicines are often grouped as potentially inappropriate for use in the elderly due to their strong anticholinergic effects.⁶

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.² Anticholinergic effects of medicines in a patient's medicines regimen may be additive, constituting anticholinergic "burden" or "load".⁷ Anticholinergic burden has been associated with cognitive impairment,^{1,8-12} confusion,¹³ falls,^{7,14,15} fractures,¹⁶ hospital admission^{7,16} and duration of admission,^{7,17} impairment in activities of daily living,⁹ poorer quality of life,¹ depression,^{1,9} incident cardiovascular disease,¹⁸ and mortality.^{11,18}

We have previously conducted two studies of anticholinergic medicines use by older Australians: a retrospective analysis of prescribing records linked to survey data from a community based female cohort;¹⁹ and an analysis of the medicines regimens of patients at baseline in a trial of peer education of general practitioners (GPs).¹ 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'.^{1,19} 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 paper 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 program and may choose to consent to their data being also used for research purposes.

Registrars spend at least three six-month full-time-equivalent terms in general practice settings. This is the compulsory general practice component of their three-year training program. During this general practice component, registrars effectively operate as

independent practitioners, though having recourse to the advice and assistance of experienced clinical supervisors. This independence includes prescribing authority (and capacity to order pathology and imaging and make specialist referrals) equivalent to other more senior GPs.

In ReCEnT, participating registrar characteristics and the characteristics of their training practice are documented. Registrars then record the details (including medicines prescribed, supplied or recommended) of sixty consecutive patient consultations, representing approximately one week of consultations, each six-month training term. Data collection is conducted around the mid-point of the term. Each prescribed, supplied or recommended medicine is linked to the problem/diagnosis for which it was prescribed, supplied or recommended.

The analyses in this study used data from ten data collection periods from 2010 to 2014. In each data collection period participating registrars each recorded 60 consultations. Individual registrars contributed data in up to three separate collection periods.

Outcome factor

The outcome factor of interest was prescribing/recommending/supplying of medicines with anticholinergic effects (hereafter referred to as ‘prescribing’). This included recommendations of over-the-counter (OTC) non-prescription medicines and direct supply of medicines (though whether it was prescription, recommendation or supply was not recorded). Medicines were coded via the Anatomic 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 review³). 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 effects⁷ and the ADS performs well in this regard compared to other anticholinergic scales.⁷ We didn’t 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 categorised 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.

Ethics approval

The ReCEnT project has approval from the University of Newcastle Human Research Ethics Committee, Reference H-2009-0323.

Results

Demographics of registrars, patients and practices

A total of 879 individual registrars (response rate 95.3%) participated over the 10 rounds of data collection, 2010-14. They each participated in one to three rounds of data collection and collectively contributed data from 1953 registrar-rounds, relating to 20,555 consultations with patients aged 65 years or older and to 35,506 problems/diagnoses.

Overall, 66.2% of the registrars were female, with a mean age of 32.6 years. Registrars who undertook their primary medical degree in Australia comprised 78.3% of participants. Participating registrar, practice and registrar-term demographics are displayed in Table 1.

Prescribing of medicines with anticholinergic effects

A total of 23,308 medicines were prescribed to patients aged 65 years or older. Of these medicines, 2,323 were ADS-defined anticholinergic medicines (10.0% of all medicines [95% CIs 9.5%-10.5%]). Level 1, Level 2 and Level 3 anticholinergic medicines comprised 8.8%, 0.05% and 1.1%, respectively, of all medicines prescribed (see Table 2).

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 (see 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 variability 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: 12.0%-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 Figure 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.¹

A singular clinical circumstance where surveillance for possible anticholinergic medicines should be especially rigorous is that of utilisation of anticholinergic drugs in patients with dementia treated with cholinesterase inhibitors. In an Australian study of this circumstance,²³ 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. While 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 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 pre-date their wide-spread 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 amongst 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 amongst 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 (though codeine was).⁷ This may reflect recent alarmingly steep increases in rates of oxycodone prescribing in Australia, especially to patients aged over 70 years.²⁵

Strengths and limitations

The study has a number of strengths. The response rate is very high for a study of GPs,²⁶ 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 don't require a doctor's prescription in Australia.

The major limitation is that our study elicits 'snapshot' data of consultation content, and we don't 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 don't 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)⁷ and the updates to the validated ADS that we used in this analysis have not been validated.

While 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.² 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.⁴ 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’. Though 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 musculoskeletal pain and that special attention on patients with traditional phenotypes may fail to detect much anticholinergic burden and, potentially, subsequent adverse clinical outcomes.

Most medicines, including anticholinergic medicines, are prescribed by GPs. While the anticholinergic adverse effects of individual ‘traditional’ high-potency anticholinergic medicines seem to be well-appreciated by GPs, the concept of ‘anticholinergic burden’ isn’t.²⁷ Our findings suggest that with the added complexity of multiple ‘invisible’ anticholinergic medicines in their patients’ regimens (across many disease chapters / body systems), GPs’ difficulties in this area may be more acute than previously appreciated. They will need support to integrate calculation of anticholinergic burden into their therapeutic

decision-making (rather than relying on knowledge of a relatively small number of obviously highly anticholinergic medicines).

Future research could aim to test interventions to alert GPs and other clinicians caring for older patients to individual patients' anticholinergic burden (and to thus prompt review of medicine regimens in response to those alerts).

Conclusions

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.

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Table 1: Demographics of participating registrars and their practices

Variable	Class	n (%) [95% CI]
Registrar variables		
(n=879)		
Registrar Gender	Male	297 (33.8) [30.7-37.0]
	Female	582 (66.2) [63.0-69.3]
Qualified as a doctor in Australia	No	189 (21.8) [19.1-24.6]
	Yes	680 (78.3) [75.4-80.9]
Registrar age (years)	Mean (SD)	32.6 (6.3)
Registrar-term or practice-term variables (n=1953)		
Registrar Training Term	Term 1	780 (39.9) [37.8-42.1]
	Term 2	698 (35.7) [33.6-37.9]
	Term 3	475 (24.3) [22.5-26.3]
Registrar worked at the practice previously	No	1394 (72.3) [70.3-74.3]
	Yes	533 (27.7) [25.7-29.7]
Registrar works fulltime	No	406 (21.3) [19.5-23.2]
	Yes	1503 (78.7) [76.8-80.6]
Does the practice routinely bulk bill	No	1610 (83.0) [81.2-84.6]
	Yes	331 (17.1) [15.4-18.8]
Number of GPs working at the practice	1-4	650 (34.1) [32.0-36.3]
	5-10+	1254 (65.9) [63.7-68.0]
Rurality of practice	Major City	1117 (57.2) [55.0-59.4]
	Inner Regional	543 (27.8) [25.9-29.8]
	Outer regional or remote	293 (15.0) [13.5-16.7]
SEIFA Index (decile) of practice	Mean (SD)	5.4 (2.9)

CI=Confidence Interval; SD=Standard Deviation

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Table 2: Anticholinergic medicines by Anticholinergic Drug Scale level - number prescribed; number of problems prescribed for; number of

Anticholinergics	Medications (n=23308) n (%) [95%CI]	Problems* (n=35506) n (%) [95%CI]	Consultations* (n=20555) n (%) [95%CI]	“Anticholinergic burden” contribution (%) [95%CI]	consultations prescribed during; contribution to ‘anticholinergic burden’
All	2323 (10.0) [9.5-10.5]	2208 (6.2) [5.9-6.6]	2136 (10.4) [9.8-11.0]	2835 (100)	
Level 1	2061 (8.8) [8.4-9.3]	1968 (5.5) [5.2-5.9]	1904 (9.3) [8.7-9.8]	2061 (72.7) [71.0-74.3]	
Level 2	12 (0.05) [0.03-0.09]	12 (0.03) [0.02-0.06]	12 (0.06) [0.03-0.1]	24 (0.8) [0.5-1.3]	
Level 3	250 (1.1) [0.9-1.2]	249 (0.7) [0.6-0.8]	247 (1.2) [1.1-1.4]	750 (26.5) [24.8-28.1]	

* an individual problem or consultation could be associated with prescription of more than one anticholinergic medicine

CI=Confidence Interval

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

level

Level 1 drugs (n=2061)	n (%)	Level 2 Drugs (n=12)	n (%)	Level 3 Drugs (n=250)	n (%)
warfarin	539 (26.15)	carbamazepine	8 (66.67)	amitriptyline	136 (54.40)
oxycodone	332 (16.11)	cyproheptadine	2 (16.67)	oxybutynin	32 (12.80)
furosemide	288 (13.97)	pethidine	2 (16.67)	promethazine	23 (9.20)
prednisolone	288 (13.97)			dosulepin	11 (4.40)
prochlorperazine	128 (6.21)			solifenacin	10 (4.00)
digoxin	77 (3.74)			doxepin	7 (2.8)
codeine	69 (3.35)			atropine	6 (2.40)
oxycodone, combinations	67 (3.25)			scopolamine	6 (2.40)
fentanyl	58 (2.81)			imipramine	5 (2.00)
morphine	56 (2.72)			benzotropine	2 (0.80)

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

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

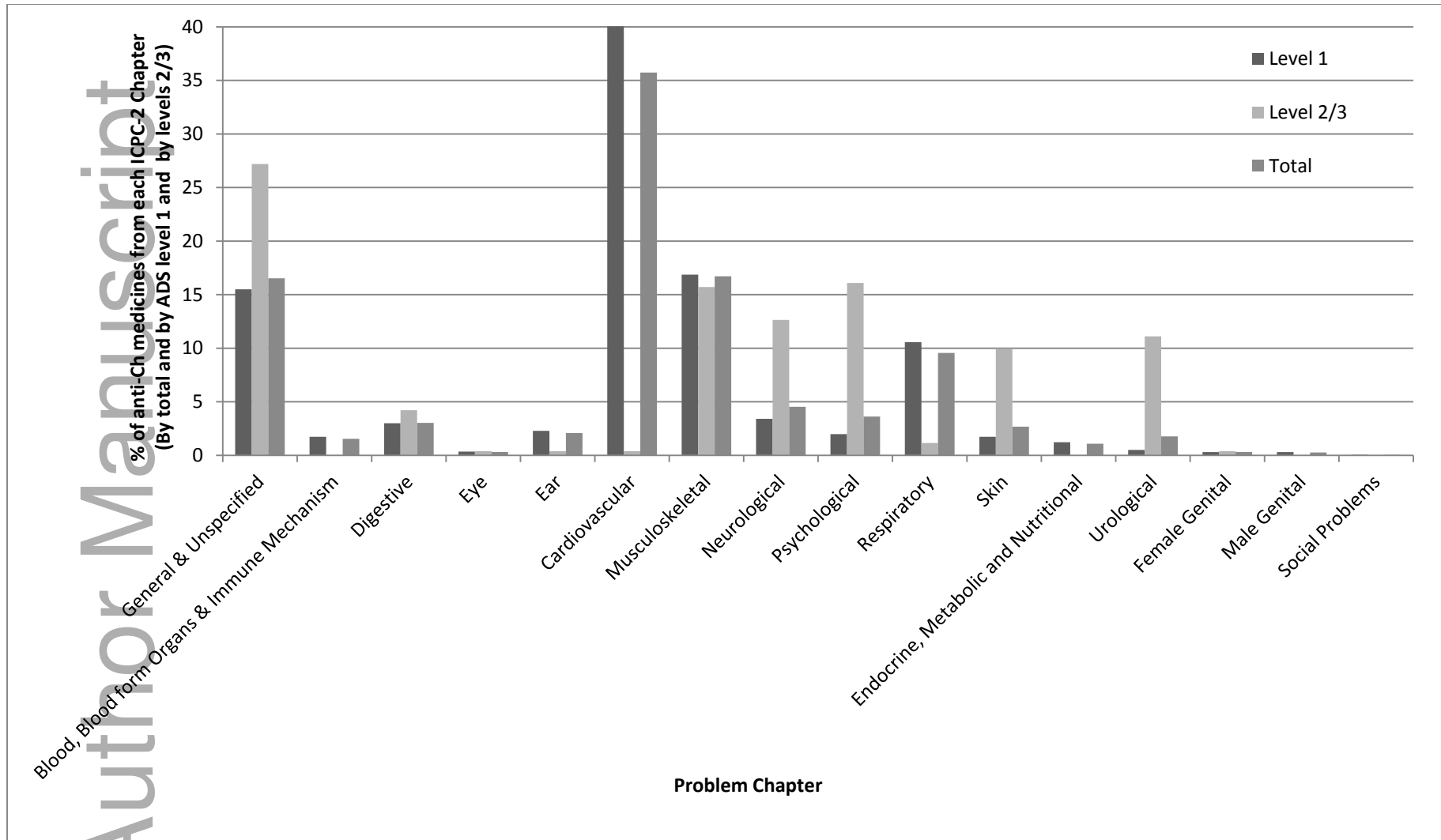
Hypertension	57 (2.9)			Osteoarthritis	4 (1.6)

* 'prescriptions' / 'renewal of medication' not presented

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Figure 1: Level 1, Level 2&3 combined, and total anticholinergic medicines, by ICPC-2 Chapter

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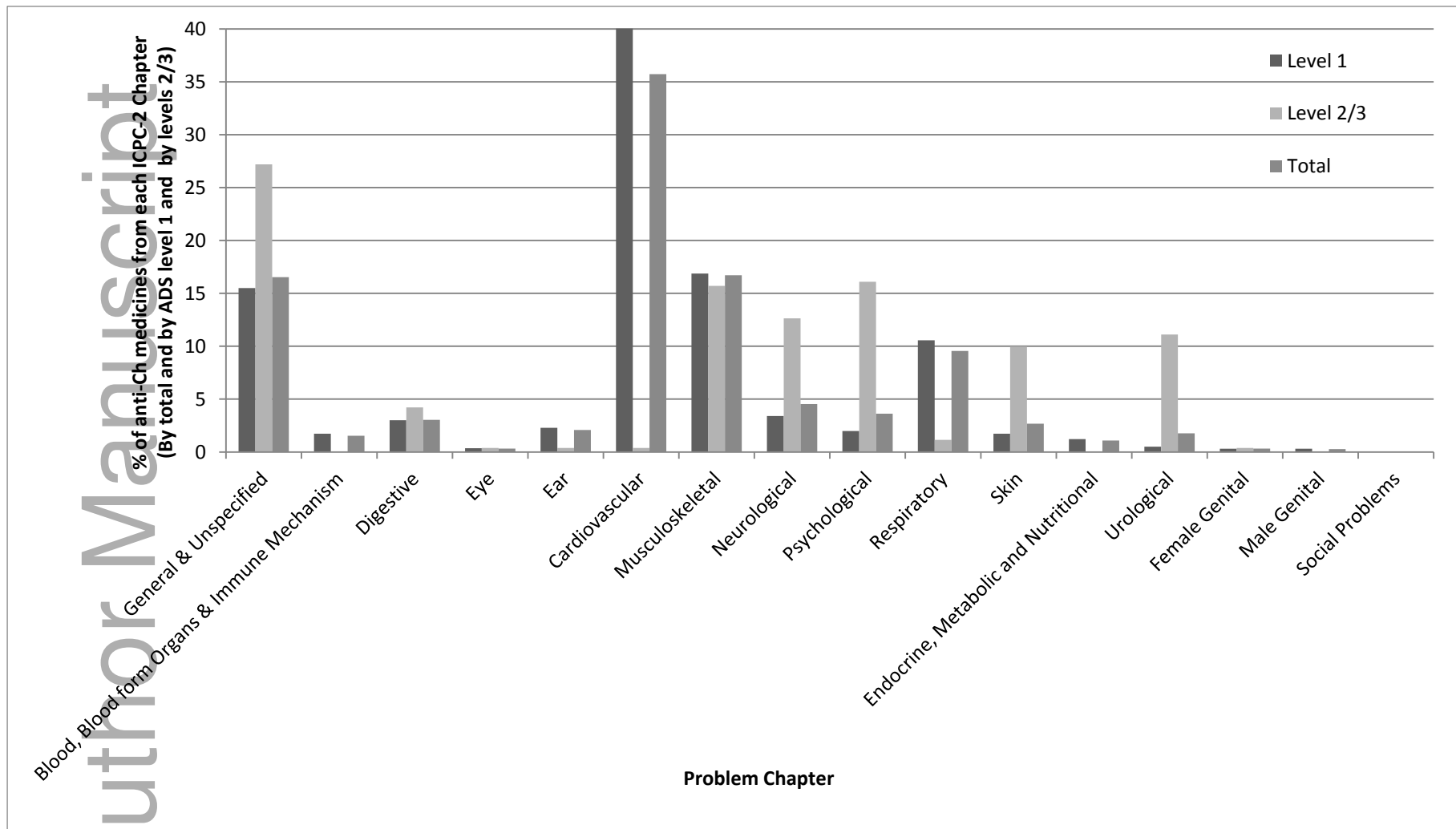


Figure 1: Level 1, Level 2&3 combined, and total anticholinergic medicines, by ICPC-2 Chapter