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Title: Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Abstract

Objectives: The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition optimal prescribing.

Design: Cross-sectional study linking anonymised computer consultations with prescription records for a 2-year time-period.

Setting: 11 general practices in North Staffordshire, England.

Participants: Study groups aged 40 years and over (N=12,875) were: (i) six chronic condition groups, (ii) combined vascular group (at least one of diabetes mellitus, cardiovascular disease or cerebrovascular disease) and (iii) non-vascular conditions with chronic obstructive pulmonary disease, osteoarthritis or depression.

Outcome Measures: Based on the British National Formulary, five main drug chapters constituted a measure of drug counts, with low count as 2 or less and high multi-drug count as 3 or more. Optimal group of drugs for COPD, OA and depression were derived from guidelines.

Results: The adjusted associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in optimal COPD drug treatment (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In depression, vascular comorbidity was associated with a reduction in optimal depression drug treatment (OR 0.6 (0.4 to 0.7)).

Conclusions: The study shows that multi-drug prescribing defined by a range of selected but different systems, is higher with comorbidity and may be associated with sub-optimal prescribing. The importance of these findings is whether such multi-drug therapy influences the outcomes of care for chronic conditions.

Article summary

Strengths and limitations of this study

- The study was based on large-scale data linking common chronic conditions from general practice populations to prescription data over a 2-year time-period.
- The study highlights the innovative approach to multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug therapy on optimal drug prescribing in populations.
- The study uses a specific but limited number of common chronic conditions to illustrate the approach to linking comorbidity and multi-drug data within a single large region of the UK.
- The study used overall broad measures of drug prescribing and further research is required to understand the specific influence of multi-drug dose and duration on longer-term outcomes.

Introduction

Comorbidity is defined as other co-occurring diseases in the same individual with an index condition, and is important concept as other conditions may influence the progression and treatment of the index condition.[1] Current evidence of the overall implications of chronic diseases, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.[2,3,4] Although the health impact of chronic disease comorbidity has been studied, there have been few studies on how chronic diseases comorbidity might influence drug use and related clinical decisions especially in general practice. This is a significant evidence gap despite the fact that drugs interventions feature routinely in many disease guidelines. Currently, the model for managing chronic diseases focuses on treating individual conditions, and patients may on the one hand benefit from the drug treatment of each of their chronic conditions; however there is a risk of multiple drug therapy, side effects and drug interactions which could in combination be detrimental.[5,6]

Many national health care policies have developed frameworks for chronic disease models of care and specific guidelines for the optimal management of chronic diseases. Examples include policy and guidelines for the common conditions in the general population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways disease and depression.[7,8,9,10,11] In addition, these guidelines are beginning to be adapted for the common experience of comorbid conditions, particularly by older people, for each of these individual conditions.[12] Since people with one or more chronic conditions are increasing in number, this has increasingly brought in focus the scale and quantity of multiple drug prescribing in general populations. The key questions then become (i) how does multiple drug prescribing relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular disease share aetiology and common drug treatment pathways, but it is still important to understand the scale of multiple drug therapy that might be associated when these conditions co-occur together in the same individual. Many chronic diseases also have conditions which are related to mechanisms other than patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and depression, and this epidemiology provides the scale of multiple drug therapies when co-occurring conditions might be un-related.

In terms of the current evidence in this field, much of it has focused around 'polypharmacy' studies.[13,14,15] However, whilst this might seem an appropriate broad umbrella term, in research and clinical approaches, it has often focused on multiple drugs and adverse associated events. Within this evidence, this still creates the gap of how multiple conditions link to multiple drugs prescribing, and whether comorbidity influences the optimal prescribing of an index disease.

In this study, the focus was on six common chronic conditions in the general population, which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of these chronic conditions for the purpose of the study is based on a number of factors including the epidemiology, especially prevalence of the diseases, as well as aetio-pathogenesis and impacts on quality of life and psychological well-being. For example, while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a common pathological basis of causation (the 'vascular group'), and often co-exist in one patient, they are also known to have high mortality rates - hence the drive towards measures aimed at optimising the management of these disease.[16,17] The other three, non-vascular chronic conditions - Chronic Obstructive Pulmonary Disease, Osteoarthritis and Depression are leading causes of morbidity, high cost of care and psychological distress respectively.[18,19,20] In addition to investigating the relative multiple drugs prescribing in comorbidity compared to one of the six index examples, there was also a test of whether comorbidity influenced optimal drug prescribing.

Methods

Design and Study population: The cross-sectional study was conducted using two linked databases on patients aged 40 years and over presenting to general practice over a 2-year time period (from 1st January 2002 to 31st December 2003).

Settings: The clinical and prescription databases analysed were derived from an anonymised computer recorded consultations from eleven general practices from the North Staffordshire Keele GP research partnership. The partnership covers a range of practices covering varying socioeconomic groups within rural and urban areas and has been involved in data collection over time for the purpose of epidemiological studies. There is an on-going process of data validation to improve data quality, and there is

evidence that this measure improves data recording by general practitioners and their teams.[21]

Chronic disease data: The Consultation in Primary Care Archive (CiPCA) database focuses on the routinely collected morbidity encounters in actual consultations and coded using a standard clinical classification (Read codes).[22] Patients who had a record of a disease-specific READ coded morbidity of interest were included in the study and the main codes were used with all associated "daughter codes". The main READ codes that were used to define the chronic disease groups were: diabetes mellitus (Read codes C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58), excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and depression (E11, E20, Eu and excluding psychosis).

Study groups: definitions

The patients were classified into the individual condition groups, and then two specific study groups were constructed: vascular group (population with at least one of diabetes mellitus, cardiovascular disease or cerebrovascular disease) and non-vascular group of individual conditions (chronic obstructive pulmonary disease, osteoarthritis or depression). The individual groups enabled the comparison of index groups to those with comorbidity. The vascular group were likely to be on similar multiple drugs, so a separate hypothesis was tested, that was prescribing in vascular conditions overall may influence prescribing in the individual non-vascular conditions of chronic obstructive pulmonary disease, osteoarthritis and depression.

Comorbidity: definitions

There were two approaches to defining comorbidity. First, comorbidity was defined as the presence of one of the other five selected conditions. So using the diabetes population as an example, the diabetes 'index' group was defined as diabetes 'alone' and without anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at least one of the other five conditions. This definition was applied to each of the six chronic conditions individually. Second, in the vascular group, comorbidity was defined separately as the individual and specific addition of COPD, OA or depression, and irrespective of whether the latter three occurred together.

The approach taken to looking at specific groups and conditions was based on a combination of clinical rationale and feasibility. Whilst, one could have investigated any number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the "Vascular" level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be over-lapping of drug treatments. However, the "non-vascular" group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group-level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups.

Prescribed drug measure: overall multi-drug count definitions

The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification.[23] The BNF consists of 15 main chapters based on the systems of the body, and within which there are further sub-sections for specific clinical indications. Only patients on repeat drug prescriptions were selected for defining measures because this gives a better representation of multiple drugs used on a long term basis for the majority of patients with chronic conditions.

Specific drug treatment chapters for the six chronic diseases of interest in the study were identified and used as a summary of multi-drug counts. The BNF chapter for cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6, and for osteoarthritis under chapters 4 and 10. This means that overall; there were five main BNF chapters, which could constitute a measure of drug counts of up to a total of 5. The multi-drug count definition in this approach would specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

Prescribed drug measure: optimal drug definitions

Optimal drug treatment for the specific conditions of COPD, OA and depression was also investigated. Whilst optimal drug treatment of these conditions can be examined in different ways such as the use of specific drugs, or drug doses and duration of drug therapy, we wanted to first establish the simplest likelihood of a patient given an optimal group of drugs for COPD, OA or depression. The optimal group of drugs derived from

guidelines for COPD[10] included bronchodilators, corticosteroids, inhaled steroids, mucolytics (BNF sections 3.1, 3.2, 3.5 and 3.6). The optimal group of drugs for osteoarthritis[24] included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The optimal group of drugs for depression[11] included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and 4.3).

Analysis

The first analyses was to describe the 2-year period prevalence of the 5 main BNF chapters in the specified chronic disease population, with a focus on some of the common drugs that were prescribed within each chapter expressed as drug prevalence/10,000 population aged 40 years and over. The five main chapter drug categories prevalence are described by age, gender and deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD) which is a composite score that is linked to postal address codes.[25] The IMD score was categorised into the bottom 20% (most deprived), middle 60% and the top 20% score (most affluent).

For each of the six chronic conditions, associations between the comorbid groups and higher multi-drug counts were compared to the respective reference 'alone' group. The 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and compared to 2 counts or less. Associations were expressed as Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios comparing prevalence of each drug count category in the comorbid group compared to the 'alone' group. Then for the vascular group, associations between each of the comorbid group with COPD, OA or depression were compared to the vascular 'alone' alone and higher multi-drug counts were then estimated.

Finally, the data was analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD and at least one of the vascular conditions; OA with at least one of the vascular conditions; and depression with at least one of the vascular conditions. Each group was the compared to their respective vascular group e.g. COPD and vascular group compared to COPD without a vascular condition, by the specific optimal drug treatment. Association estimates are presented both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were carried out using SPSS version 17.0 statistical software.

Results

Study population

In the study population of 12,875 aged 40 years and over, the 2-year time-period prevalence estimated per 10,000 for the cardiovascular system drugs was 7,289, for respiratory system drugs was 2,222, for non-opioid analgesia was 4,190, for anti-depressants was 2,517, for anti-diabetic drugs was 2,265 and musculoskeletal system anti-inflammatory drugs was 1,664 (**Table 1**).

In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% deprivation status were more likely to be prescribed all five main drug categories. For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were higher for men compared to women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD. Prevalence figures were lower for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (**Table 2**).

Individual chronic condition comorbidity and higher multi-drug counts

For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence numbers were greater for the individual groups without the other five comorbid conditions compared to the numbers for the individual conditions with comorbidity of other five conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone' ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for diabetes comorbid group.

Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

Vascular condition comorbidity and higher multi-drug counts

The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group comorbid with OA OR 3.0 (2.6 to 3.5).

Comorbid vascular conditions and optimal non-vascular condition prescribing

The three specific non-vascular groups of COPD, OA and depression were compared with comorbid vascular conditions to without such vascular comorbidity in terms of their respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation, the association between the COPD and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared to their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).

Discussion

Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years and over with one of six specified and common chronic conditions showed the scale of multi-drug prescribing, which was higher in the presence of comorbidity compared to the respective index groups. Whilst previous evidence has shown the high levels of 'polypharmacy'[15], our study findings link the disease status, comorbidity status to the measure of multi-drug prescribing. Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or the non-vascular (COPD, OA or depression), the higher levels of multi-drug prescribing varied. All six conditions with comorbidity compared to their index condition had much higher multi-drug count, even

adjusting for age, gender and deprivation. The measure of multi-drug count was notably distinct by the use of five different main drug chapter categories which were for different body systems, which means that this 'outcome' was not about multiple drugs use for the same condition. For example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different and distinct body systems, and not to the different drugs under the same chapter. The chronic condition of depression comorbidity had the strongest strength of association with higher multi-drug counts, followed by cardiovascular disease comorbidity, and the estimates of association for cerebrovascular disease, osteoarthritis and diabetes were similar. These findings suggest that the index condition and comorbidity may influence the range of multi-drug prescribing, and generates the interesting hypothesis on the potential variation in clinical outcomes of the index conditions may be because of underlying comorbid drug prescribing.

The study also grouped the vascular-related conditions to investigate the influence of non-vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of COPD, OA or depression). Again, the adjusted associations were significant, with vascular comorbidity being associated with higher-multi-drug counts compared to the respective 'vascular index' group. Here the clinical implication is that vascular comorbidity in populations aged 40 years and over might not only be associated with multiple vascular drugs as routinely suggested by clinical guidelines[26], but by a range of conditions such as comorbidity of COPD, OA or depression. It is possible that these conditions and the drug treatments for them may also in the end influence the health and healthcare outcomes of the index vascular conditions.[27]

In terms of the influence of comorbidity on optimal drug prescribing, our study findings show that vascular comorbidity in COPD and depression is associated with sub-optimal drug prescribing for the respective conditions of COPD and depression. Similar findings, particularly for sub-optimal depression drug treatment, when depression is comorbid with chronic disease has been shown previously.[28,29] However, such findings for osteoarthritis were not found, and here it is possible that the 'outcome' of analgesia was too broad, as analgesia use covers a range of other painful conditions, in addition to osteoarthritis. Although the optimal drug definition was simple and broad, our study findings seem to suggest that comorbidity does influence optimal drug prescribing, and further reasons for this might dis-entangle whether it is due to drug therapeutic or diagnostic conflicts.

The large scale study of specified chronic diseases was conducted using an anonymised database for a 2-year time-period. In terms of the cross-sectional associations, the findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer clinical implications as outlined earlier. However, the implications of the associations

between comorbidity and optimal drug definitions may be limited in this cross-sectional design and these may be treated cautiously as emergent findings. The chronic disease definitions were also based on routinely collected registers from general practices, which were and are part of a research network dedicated to the collection of clinical data in actual consultation. Whilst these chronic disease registers may be subject to variations in recording[30], the study analyses provide the estimates of association in actual clinical practice across 11 different sites. The drug definitions were based on routinely coded repeat prescriptions and over a 2-year time-period represent an appropriate measure at the broad system category. Most of these drugs, other than analgesia such as anti-inflammatories, are not available over the counter and are usually clinician prescribed. So it is possible that common over the counter drugs, particularly in relation to osteoarthritis, may be an under-estimate; however, the selection of repeated prescribing would mitigate against such under-estimation. Finally, although a large scale study, these general practices are drawn from one region of England, and whilst this might limit generalisability, the internal validity of the findings still remains.

In conclusion, our study findings show the links between common chronic conditions, comorbidity and associated multi-drug prescribing. The key and distinct finding is that the study shows that multi-drug prescribing defined by a range of selected but different systems is high in chronic conditions and higher in comorbidity. The common group of vascular conditions are not the only ones associated with their 'own' guideline driven multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and depression adds to the multi-drugs burden in patients. The importance of these findings, in addition to quantifying the scale, is whether such multi-drug therapy influences the quality of care for each of the individual conditions. Our findings suggest the potential for sub-optimal drug treatment as a consequence in line with other evidence[31], but further research is required to investigate the impact of disease status, comorbidity, multi-drug therapy on prospective and long-term outcomes of clinical care.

Table 1: Prescribed drug prevalence by BNF main chapter and specific sections

BNF Chapter	BNF subsections	BNF Classification	Drug examples	Number	Drug prevalence/ 10,000†
2 Cardiovascular system				9384	7289
	2.9	Antiplatelet drugs	Aspirin, Clopidogrel Dipyridamole	*5044*	*3918*
	2.8	Anticoagulants	Warfarin	*669*	*520*
	2.2	Diuretics	Thiazide diuretics	*4912*	*3815*
	2.4	Beta blockers	Bisoprolol	*4034*	*3133*
	2.5	*ACE Inhibitors or *ARB	Ramipril, candesartan	*4250*	*3301*
	2.6	Nitrates, Calcium antagonists	GTN, Amlodipine	*4984*	*3817*
	2.12	Lipid regulating drugs	Simvastatin	*4894*	*3801*
3 Respiratory system				*2861*	2222
	3.1	Bronchodilators	Salbutamol	*2775*	*2155*
	3.2	Corticosteroids	Beclomethasone	*2140*	*1662*
	3.5	Respiratory stimulants	Doxapram	*0*	0
	3.6	Oxygen		*94*	73
4 Central nervous system drugs				*7478*	5808
	4.7.1	Non-Opioid analgesics	Paracetamol	*5395*	*4190*
	4.7.2	Opioid analgesics	Codeine,Tramadol	*855*	*664*
	4.1	Hypnotics and anxiolytics	Diazepam	*1180*	917
	4.3	Selective Serotonin Reuptake Inhibitors Tricyclic Antidepressants	Fluoxetine, Citalopram, Amitriptyline	*3241*	2517

6 Endocrine system				*2916*	2265
	6.1.1	Insulin	Insulin, Humalog	*632*	*491*
	6.1.2	Oral anti-diabetic drugs	Metformin, Gliclazide	*2334*	*1805*
10 Musculoskeletal and joint disease				*2143*	1664
	10.1.1	Non-steroidal anti-inflammatory drugs	Ibuprofen, cyclooxygenase inhibitors	*2143*	*1664*

†*Population refers to those with one of six chronic conditions (n* = 12875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF)

Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				
		Cardiovascular system	Respiratory System[1]	Central-nervous System[2]	Endocrine System[3]	Musculo-skeletal System[4]
Age (years)						
40-54	2738	1257 (46)	441 (16)	1447 (53)	555 (20)	378 (14)
55-69	4963	3712 (75)	1131 (23)	2694 (54)	1250 (25)	1003 (20)
70-84	4459	3807 (85)	1154 (26)	2824 (63)	1010 (23)	703 (16)
85 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
Gender						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
Deprivation**						
Deprived status	2609	1952 (75)	780 (30)	1705 (65)	695 (27)	474 (18)
Middle status	7228	5308 (73)	1538 (21)	4184 (58)	1616 (22)	1223 (17)
Affluent status	2203	1584 (72)	354 (16)	1185 (54)	419 (19)	377 (17)

***Deprivation measured by Index of Multiple of Deprivation, figures in brackets refer to the percentage of each study factor sub-group*

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Diabetes 'alone'	239	1178	4332	3120	1021	110	1.0
Diabetes comorbidity	58	492	2208	4523	2353	366	3.50 (3.0-4.2)
Prevalence ratio	*0.2*	*0.4*	*0.5*	*1.5*	*2.3*	*3.3*	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
Prevalence ratio	*0.2*	*0.3*	*0.9*	*2.6*	*8.3*	*7.6*	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
Prevalence ratio	*0.1*	*0.4*	*1.1*	*2.5*	*9.7*	*n/a*	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
Prevalence ratio	*0.20*	*0.4*	*0.8*	*1.5*	*5.00*	*n/a*	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
Prevalence ratio	*0.1*	*0.5*	*1.0*	*1.8*	*5.2*	*54*	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
Prevalence ratio	*0.17*	*0.34*	*1.15*	*4.58*	*13.7*	*n/a*	

**Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, **Comorbid drug ratio = 2-year drug count prevalence in the comorbid group/2-year drug count prevalence in the disease alone group; adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease*

Table 4: Associations between vascular comorbidity groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Vascular group only*	199	2373	4018	2547	773	89	1.0
Vascular group and COPD	85	677	2854	4207	2008	169	4.63 (3.8-5.7)
Prevalence ratio	*0.43*	*0.29*	*0.71*	*1.65*	*2.60*	*1.90*	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
Prevalence ratio	*0.15*	*0.37*	*0.87*	*1.45*	*2.01*	*3.92*	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
Prevalence ratio	*0.35*	*0.35*	*0.93*	*1.54*	*1.76*	*1.03*	

**Vascular group only is the reference group without COPD, OA or depression; prevalence ratio is comparing vascular comorbid group with vascular group alone for each drug count category, adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less)*

Table 5: Optimal drug treatment of non-vascular conditions in vascular comorbidity

Numbers (%)	Optimal drug treatment		Unadjusted	Adjusted
	No	Yes	Odds Ratio (95% CI)	Odds Ratio (95% CI)
COPD without vascular comorbidity	123 (22)	937 (88)	1.0	1.0
COPD and vascular comorbidity	87 (19)	382 (81)	0.58 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

***Optimal drug treatment for COPD, OA or depression respectively, adjusted for age, gender and deprivation as measured by Index of Multiple deprivation*

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Contributorship Statement

ER and DG coordinated the study data collection and contributed to the writing of the manuscript. ER, DG and UTK were involved in study design and developed the statistical approaches. UTK conceived and designed the study, was involved with analysis, interpretation and contributed to the writing of this manuscript. All authors have contributed and approved the final version of this manuscript

Competing Interests

None

Data sharing statement

Data is not available for sharing under existing governance arrangements.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Title: Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Abstract

Objectives: The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition optimal prescribing.

Design: Cross-sectional study linking anonymised computer consultations with prescription records for a 2-year time-period.

Setting: 11 general practices in North Staffordshire, England.

Participants: Study groups aged 40 years and over (N=12,875). Within six conditions, comorbid group with the other 5 conditions was compared to an 'alone' group without them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and cerebrovascular disease) comorbidity influenced COPD, OA or depression drug prescribing was investigated.

Outcome Measures: Based on the British National Formulary, five main drug chapters constituted a measure of drug counts, with low count as 2 or less and high multi-drug count as 3 or more. Key drugs prescribed for COPD, OA and depression were derived from guidelines.

Results: The adjusted associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in key COPD drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In depression, vascular comorbidity was associated with a reduction in key depression drug treatments (OR 0.6 (0.4 to 0.7)).

Conclusions: Our findings show multi-drug prescribing for different body systems is higher with comorbidity and may be associated with lower likelihood of prescribing for specific conditions. Further research is required on whether multi-drug prescribing influences the outcomes of care for chronic conditions.

Article summary

Strengths and limitations of this study

- The study was based on large-scale data linking common chronic conditions from general practice populations to prescription data over a 2-year time-period.
- The study highlights the innovative approach to multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug therapy on potentially 'optimal' drug prescribing in populations.
- The study uses a specific but limited number of common chronic conditions to illustrate the approach to linking comorbidity and multi-drug data within a single large region of the UK.
- The study used overall broad measures of drug prescribing and further research is required to understand the specific influence of multi-drug dose and duration on longer-term outcomes.

Introduction

Many older people experience two or more morbidities at the same time which is defined as multimorbidity, and within this comorbidity is defined as other co-occurring diseases in the same individual with an index condition.[1,2] These are important concepts as the experience of multiple conditions at the same time may influence the progression and treatment of an index condition. Current evidence of the overall implications of chronic diseases, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.[3,4,5] Although the health impact of chronic disease comorbidity has been studied, there have been few studies on how chronic diseases comorbidity might influence drug use and related clinical decisions especially in general practice. This is a significant evidence gap despite the fact that drug interventions feature routinely in many disease guidelines. Currently, the model for managing chronic diseases focuses on treating individual conditions, and patients may on the one hand benefit from the drug treatment of each of their chronic conditions; however there is a risk of multiple drug therapy, side effects and drug interactions which could in combination be detrimental.[6,7]

Many national health care policies have developed frameworks for chronic disease models of care and specific guidelines for the optimal management of chronic diseases. Examples include policy and guidelines for the common conditions in the general population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways disease and depression.[8,9,10,11,12] In addition, these guidelines are beginning to be adapted for the common experience of comorbid conditions, particularly by older people, for each of these individual conditions.[13] Since people with one or more chronic conditions are increasing in number, this has increasingly brought in focus the scale and quantity of multiple drug prescribing in general populations. The key questions then become (i) how does multiple drug prescribing for different systems relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular disease share aetiology and common drug treatment pathways, but it is still important to understand the scale of multiple drug therapy that might be associated when these conditions co-occur together in the same individual. Many chronic diseases also have conditions which are related to mechanisms other than patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

depression, and this epidemiology provides the scale of multiple drug therapies when co-occurring conditions might be un-related.

In terms of the current evidence in this field, much of it has focused around 'polypharmacy' studies.[14,15,16] However, whilst this might seem an appropriate broad umbrella term, in research and clinical approaches, it has often focused on arbitrarily chosen number of drugs, and linked the term to either inappropriate prescribing or associated adverse events in older populations.[16] This lack of consensus defined approach to this problem has led to an argument for less ambiguous terminology[17], and we propose that 'multi-drug' therapy is used to link in with the standard approach to two or more conditions, which is 'multi-morbidity'. Within this evidence, there is still a clear gap in how morbidity link to drug prescribing, and whether comorbidity influences the drug prescribing for an index disease.

In this study, the focus was on six common chronic conditions in the general population, which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of these chronic conditions for the purpose of the study was based on a number of factors including the epidemiology, especially prevalence of the diseases, as well as aetio-pathogenesis and impacts on quality of life and psychological well-being. For example, while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a common pathological basis of causation (the 'vascular group'), and often co-exist in one patient, they are also known to have high mortality rates - hence the drive towards measures aimed at optimising the management of these diseases.[18,19] The other three, non-vascular chronic conditions - chronic obstructive pulmonary disease (COPD), osteoarthritis (OA) and depression are leading causes of morbidity, high cost of care and psychological distress respectively. [20,21,22] The rationale for our focus on few selected common conditions was also to provide common comorbidity combinations which are potentially treated with drugs as a key intervention.

We investigated two separate issues using the selected group of vascular and non-vascular conditions. First, we wanted to investigate the relative multi-drug prescribing for each of six chosen index examples, comparing comorbid groups with prescribing levels in the respective index groups. Second, we wanted to test of whether vascular comorbidity influenced key drug prescribing for chosen conditions. The vascular group were likely to be on similar multiple drugs, so the distinct hypothesis was tested, that was drug

prescribing in vascular conditions overall may influence key drug prescribing in the individual non-vascular conditions of COPD, OA or depression.

Methods

Design and Study population: The cross-sectional study was conducted using two linked databases on patients aged 40 years and over presenting to general practice over a 2-year time period (from 1st January 2002 to 31st December 2003). We wanted to investigate what multi-drug prescribing levels were before a national UK performance-based incentive (Quality outcomes Framework) was implemented to test the associations between comorbidity and routine multi-drug prescribing. Ethical approval for the use of these anonymised databases was granted by the North Staffordshire Research Ethics Committee

Settings: The clinical and prescription databases analysed were derived from an anonymised computer recorded consultations from eleven general practices from the North Staffordshire Keele GP research partnership. The partnership covers a range of practices covering varying socioeconomic groups within rural and urban areas and has been involved in data collection over time for the purpose of epidemiological studies. There is an on-going process of data validation to improve data quality, and there is evidence that this measure improves data recording by general practitioners and their teams.[23]

Chronic disease data: The Consultation in Primary Care Archive (CiPCA) database focuses on the routinely collected morbidity encounters in actual consultations and coded using a standard clinical classification (Read codes).[24] Patients who had a record of a disease-specific READ coded morbidity of interest were included in the study and the main codes were used with all associated "daughter codes". The main READ codes that were used to define the chronic disease groups were: diabetes mellitus (Read codes C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58), excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and depression (E11, E20, Eu and excluding psychosis).

Comorbidity: definitions

There were two approaches to defining comorbidity. First, comorbidity was defined as the presence of one of the other five selected conditions. So using the diabetes population as

an example, the diabetes 'index' group was defined as diabetes 'alone' and without anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at least one of the other five conditions. The index 'alone' group would also enable the capture of the other morbidity that was outside of the study selected conditions. This definition was applied to each of the six chronic conditions individually. Second, in the vascular group, comorbidity was defined separately as the individual and specific addition of COPD, OA or depression, and irrespective of whether the latter three occurred together.

Prescribed drug measure: overall multi-drug count definitions

The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification.[25] The BNF consists of 15 main chapters based on the systems of the body, and within which there are further sub-sections for specific clinical indications. Only patients on repeat drug prescriptions were selected for defining measures because this gives a better representation of multiple drugs used on a long term basis for the majority of patients with chronic conditions.

Specific drug treatment chapters for the six chronic diseases of interest in the study were identified and used as a summary of multi-drug counts. The BNF chapter for cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6, and for osteoarthritis under chapters 4 and 10. This means that overall; there were five main BNF chapters, which could constitute a measure of drug counts of up to a total of 5. The multi-drug count definition in this approach would then specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

Vascular comorbidity and drug prescribing for non-vascular conditions

The key likelihood of receiving drug treatments for the specific conditions of COPD, OA and depression in the study population with vascular comorbidity was also investigated. In this approach the 'vascular' comorbidity was defined as the group any one of diabetes, cardiovascular disease and cerebrovascular disease. The non-vascular groups were then individually compared with and without vascular comorbidity. For example, the COPD group was compared with vascular comorbidity to the COPD without vascular comorbidity, in relation to the likelihood of receiving COPD-specific drug treatment.

Whilst the key drug treatments for COPD, OA and depression can be examined in different ways such as the use of specific drugs, or drug doses and duration of drug therapy, we wanted to first establish the simplest likelihood of a patient given any one of the key group of drugs for COPD, OA or depression. The group of drugs derived from guidelines for COPD[10] included bronchodilators, corticosteroids, inhaled steroids and oxygen(BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for osteoarthritis[26] included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for depression[11] included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and 4.3).

Analysis

The first analyses was to describe the 2-year period prevalence of the 5 main BNF chapters in the specified chronic disease population, with a focus on some of the common drugs that were prescribed within each chapter expressed as drug prevalence/10,000 population aged 40 years and over, and differences were assessed using Chi-square tests. The five main chapter drug categories prevalence are described by age, gender and deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD) which is a composite score that is linked to postal address codes.[27] The IMD score was categorised into the bottom 20% (most deprived), middle 60% and the top 20% score (most affluent).

For each of the six chronic conditions, associations between the comorbid groups and higher multi-drug counts were compared to the respective reference 'alone' group. The 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and compared to 2 counts or less. Associations using logistic regression were expressed as Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios comparing prevalence of each drug count category in the comorbid group compared to the 'alone' group. Then for the vascular group, associations between each of the comorbid group with COPD, OA or depression were compared to the vascular 'alone' alone and higher multi-drug counts were then estimated.

Finally, the data was analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD and at least one of the vascular conditions; OA with at least one of the vascular conditions; and depression with at least one of the vascular conditions. Each group was the compared to their respective

vascular group e.g. COPD and vascular group compared to COPD without a vascular condition, by the specific optimal drug treatment. Association estimates using logistic regression are presented both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were carried out using SPSS version 17.0 statistical software.

Results

Study population

In the study population of 12,875 aged 40 years and over, the number of patients prescribed with cardiovascular system drugs were 9,384 (2-year time-period prevalence 73%), respiratory system drugs were 2,861 (22%), non-opioid analgesia were 5,395 (42%), anti-depressants were 3,241 (25%), anti-diabetic drugs were 2,916 (23%) and musculoskeletal system anti-inflammatory drugs were 2143 (17%) (**Table 1**).

In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% deprivation status were significantly more likely to be prescribed all main drug categories, except for the cardiovascular system (Chi-square test for trend $p<0.001$). For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were significantly higher for men compared to women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD ($p=0.462$). Prevalence figures were lower for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (Chi square test $p<0.001$ (**Table 2**)).

Individual chronic condition comorbidity and higher multi-drug counts

For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence numbers were greater for the individual groups without the other five comorbid conditions compared to the numbers for the individual conditions with comorbidity of other five conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone' ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for diabetes comorbid group.

Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by

strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

Vascular condition comorbidity and higher multi-drug counts

The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group comorbid with OA OR 3.0 (2.6 to 3.5).

Comorbid vascular conditions and optimal non-vascular condition prescribing

The three specific non-vascular groups of COPD, OA and depression were compared with comorbid vascular conditions to without such vascular comorbidity in terms of their respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation, the association between the COPD and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared to their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).

Discussion

Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years and over with one of six specified and common chronic conditions showed the scale of multi-drug prescribing, which was higher in the presence of comorbidity compared to the respective index groups. Whilst previous evidence has shown the high levels of multiple

drug prescribing[15], our study findings link the disease status, comorbidity status to the measure of multi-drug prescribing for different systems.

Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or the non-vascular (COPD, OA or depression), the higher levels of multi-drug prescribing varied. All six conditions with comorbidity compared to their index condition had much higher multi-drug count, even adjusting for age, gender and deprivation. The measure of multi-drug count was notably distinct by the use of five different main drug chapter categories which were for different body systems, which means that this 'outcome' was not about multiple drugs use for the same condition. For example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different and distinct body systems, and not to the different drugs under the same chapter. The chronic condition of depression comorbidity had the strongest strength of association with higher multi-drug counts, followed by cardiovascular disease comorbidity, and the estimates of association for cerebrovascular disease, osteoarthritis and diabetes were similar. These findings suggest that the index condition and comorbidity may influence the range of multi-drug prescribing, and generates the interesting hypothesis on the potential variation in clinical outcomes of the index conditions may be because of underlying comorbid drug prescribing.

The study also grouped the vascular-related conditions to investigate the influence of non-vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of COPD, OA or depression). Again, the adjusted associations were significant, with vascular comorbidity being associated with higher-multi-drug counts compared to the respective 'vascular index' group. Here the clinical implication is that vascular comorbidity in populations aged 40 years and over might not only be associated with multiple vascular drugs as routinely suggested by clinical guidelines[28], but by a range of conditions such as comorbidity of COPD, OA or depression. It is possible that these conditions and the drug treatments for them may also in the end influence the health and healthcare outcomes of the index vascular conditions.[29]

In terms of the influence of comorbidity on key drug prescribing, our study findings show that vascular comorbidity in COPD and depression is associated with lower likelihood of drug prescribing for the respective conditions of COPD and depression. Similar findings, particularly for sub-optimal depression drug treatment, when depression is comorbid with chronic disease has been shown previously.[30,31] However, such findings for osteoarthritis were not found, and here it is possible that the 'outcome' of analgesia was too broad, as analgesia use covers a range of other painful conditions, in addition to osteoarthritis.

Although the key drug definition was simple and broad, our study findings seem to

suggest that comorbidity does influence drug prescribing for specific conditions. Whether this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-disease interactions and the overall well-being of the patient is the important question raised by the findings.

The approach taken to looking at specific groups and six common conditions was based on a combination of clinical rationale and feasibility. Whilst, one could have investigated any number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the "vascular" level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be over-lapping of drug treatments. However, the "non-vascular" group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group-level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups. The study focus was also on comorbidity and further research is also required on how multimorbidity, defined as two or more conditions, influences the overall prescribing of multiple drugs and when the unit of analysis for outcome is not the disease but the arguably more important patient-centred outcomes.

The large scale study of specified chronic diseases was conducted using an anonymised database for a 2-year time-period. In terms of the cross-sectional associations, the findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer clinical implications as outlined earlier. However, the implications of the associations between comorbidity and the key drug definitions may be limited in this cross-sectional design and these may be treated cautiously as emergent findings. The chronic disease definitions were also based on routinely collected registers from general practices, which were and are part of a research network dedicated to the collection of clinical data in actual consultation. Whilst these chronic disease registers may be subject to variations in recording[32], the study analyses provide the estimates of association in actual clinical practice across 11 different sites.

The drug definitions were based on routinely coded repeat prescriptions and over a 2-year time-period represent an appropriate measure at the simpler but distinct broad system category. Patients however will also have been prescribed other drug categories outside of the five main categories that we had selected and for other less common conditions from the ones selected in the study, which means these drug levels are a specific estimate. The construction of our study defined index or 'alone' groups (without the other

5 conditions) provided the relative multi-drug level estimates to when the index condition was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone' group provide an estimate of main drug system prescribing without the associated condition (i.e. for other indications) compared to levels when there is a clear comorbidity record. However, this is time-defined by a 2-year time window, so some mis-classification may be possible and further research could explore how broad system drug definitions capture the underlying and specific common diagnostic categories. Further research is also required for the arguably more complex assimilation of the range of defined drug categories, other multi-morbidity and to investigate specific effect of individual drugs categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not available over the counter and are usually clinician prescribed. So it is possible that common over the counter drugs, particularly in relation to osteoarthritis, may be an under-estimate; however, the selection of repeated prescribing would mitigate against such under-estimation. Finally, although a large scale study, these general practices are drawn from one region of England, and whilst this might limit generalisability, the internal validity of the findings still remains.

In conclusion, our study findings show the links between common chronic conditions, comorbidity and associated multi-drug prescribing. The key and distinct finding is that the study shows that multi-drug prescribing defined by a range of selected but different systems is high in chronic conditions and higher in comorbidity. The common group of vascular conditions are not the only ones associated with their 'own' guideline driven multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and depression adds to the multi-drugs burden in patients. The importance of these findings, in addition to quantifying the scale, is whether such multi-drug therapy influences the quality of care for each of the individual conditions. Our findings suggest the potential for sub-optimal drug treatment as a consequence is in line with other evidence[33], but further research is required to investigate the impact of disease status, comorbidity, multi-drug therapy on prospective and long-term outcomes of clinical care.

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Data sharing: Data is not available for sharing under existing governance arrangements and no additional data is available.

Table 1: Prescribed drug prevalence by BNF main chapter and specific sections

BNF Chapter	BNF subsections	BNF Classification	Drug examples	Number	Drug prevalence/ 10,000†
2 Cardiovascular system				9384	7289
	2.9	Antiplatelet drugs	Aspirin, Clopidogrel Dipyridamole	*5044*	*3918*
	2.8	Anticoagulants	Warfarin	*669*	*520*
	2.2	Diuretics	Thiazide diuretics	*4912*	*3815*
	2.4	Beta blockers	Bisoprolol	*4034*	*3133*
	2.5	*ACE Inhibitors or *ARB	Ramipril, candesartan	*4250*	*3301*
	2.6	Nitrates, Calcium antagonists	GTN, Amlodipine	*4984*	*3817*
	2.12	Lipid regulating drugs	Simvastatin	*4894*	*3801*
3 Respiratory system				*2861*	2222
	3.1	Bronchodilators	Salbutamol	*2775*	*2155*
	3.2	Corticosteroids	Beclomethasone	*2140*	*1662*
	3.6	Oxygen	n/a	*94*	73
4 Central nervous system drugs				*7478*	5808
	4.7.1	Non-Opioid analgesics	Paracetamol	*5395*	*4190*
	4.7.2	Opioid analgesics	Codeine,Tramadol	*855*	*664*
	4.1	Hypnotics and anxiolytics	Diazepam	*1180*	917
	4.3	Selective Serotonin Reuptake Inhibitors Tricyclic Antidepressants	Fluoxetine, Citalopram, Amitriptyline	*3241*	2517
6 Endocrine system				*2916*	2265
	6.1.1	Insulin	Insulin, Humalog	*632*	*491*
	6.1.2	Oral anti-diabetic drugs	Metformin, Gliclazide	*2334*	*1805*

10 Musculoskeletal and joint disease				*2143*	1664
	10.1.1	Non-steroidal anti-inflammatory drugs	Ibuprofen, cyclooxygenase inhibitors	*2143*	*1664*

†*Population refers to those with one of six chronic conditions (n* = 12875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF) classification

Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	Musculo-skeletal System
Age (years)						
40-54	2738	1257 (46)	441 (16)	1447 (53)	555 (20)	378 (14)
55-69	4963	3712 (75)	1131 (23)	2694 (54)	1250 (25)	1003 (20)
70-84	4459	3807 (85)	1154 (26)	2824 (63)	1010 (23)	703 (16)
85 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
Gender						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
Deprivation**						
Deprived status	2609	1952 (75)	780 (30)	1705 (65)	695 (27)	474 (18)
Middle status	7228	5308 (73)	1538 (21)	4184 (58)	1616 (22)	1223 (17)
Affluent status	2203	1584 (72)	354 (16)	1185 (54)	419 (19)	377 (17)

***Deprivation measured by Index of Multiple of Deprivation, figures in brackets refer to the percentage of each study factor sub-group*

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Diabetes 'alone'	239	1178	4332	3120	1021	110	1.0
Diabetes comorbidity	58	492	2208	4523	2353	366	3.50 (3.0-4.2)
Prevalence ratio	*0.2*	*0.4*	*0.5*	*1.5*	*2.3*	*3.3*	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
Prevalence ratio	*0.2*	*0.3*	*0.9*	*2.6*	*8.3*	*7.6*	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
Prevalence ratio	*0.1*	*0.4*	*1.1*	*2.5*	*9.7*	*n/a*	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
Prevalence ratio	*0.20*	*0.4*	*0.8*	*1.5*	*5.00*	*n/a*	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
Prevalence ratio	*0.1*	*0.5*	*1.0*	*1.8*	*5.2*	*54*	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
Prevalence ratio	*0.17*	*0.34*	*1.15*	*4.58*	*13.7*	*n/a*	

**Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, **Comorbid drug ratio = 2-year drug count prevalence in the comorbid group/2-year drug count prevalence in the disease alone group; adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease*

Table 4: Associations between vascular comorbidity groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Vascular group only*	199	2373	4018	2547	773	89	1.0
Vascular group and COPD	85	677	2854	4207	2008	169	4.63 (3.8-5.7)
Prevalence ratio	*0.43*	*0.29*	*0.71*	*1.65*	*2.60*	*1.90*	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
Prevalence ratio	*0.15*	*0.37*	*0.87*	*1.45*	*2.01*	*3.92*	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
Prevalence ratio	*0.35*	*0.35*	*0.93*	*1.54*	*1.76*	*1.03*	

**Vascular group only is the reference group without COPD, OA or depression; prevalence ratio is comparing vascular comorbid group with vascular group alone for each drug count category, adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less)*

Table 5: Key drug treatment of non-vascular conditions in vascular comorbidity

Numbers (%)	Key drug treatments		Unadjusted	Adjusted
	No	Yes	Odds Ratio (95% CI)	Odds Ratio (95% CI)
COPD without vascular comorbidity	123 (22)	937 (88)	1.0	1.0
COPD and vascular comorbidity	87 (19)	382 (81)	0.58 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

***Drug treatment for COPD, OA or depression respectively, adjusted for age, gender and deprivation as measured by Index of Multiple deprivation*

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Title: Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Abstract

Objectives: The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition optimal prescribing.

Design: Cross-sectional study linking anonymised computer consultations with prescription records for a 2-year time-period.

Setting: 11 general practices in North Staffordshire, England.

Participants: ~~Study groups~~Study population was aged 40 years and over (N=12,875~~) were: (i) six chronic condition groups, (ii) combined vascular group (at least one of diabetes mellitus, cardiovascular disease or cerebrovascular disease) and (iii) non-vascular conditions with chronic obstructive pulmonary disease, osteoarthritis or depression~~). Within six conditions, comorbidity with the other 5 conditions was compared to index 'alone' group without them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and cerebrovascular disease) comorbidity influenced COPD, OA or depression drug prescribing was investigated.

Outcome Measures: Based on the British National Formulary, five main drug chapters constituted a measure of drug counts, with low count as 2 or less and high multi-drug count as 3 or more. ~~Optimal group of~~Key drugs prescribed for COPD, OA and depression were derived from guidelines.

Results: The adjusted associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in ~~optimal~~ key COPD drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In depression, vascular comorbidity was associated with a reduction in ~~optimal~~ key depression drug treatments (OR 0.6 (0.4 to 0.7)).

Conclusions: ~~The study shows~~Our findings ~~that~~show multi-drug prescribing ~~defined by a range of selected but~~for different body systems~~,~~ is higher with comorbidity and may be associated with ~~sub-optimal~~lower likelihood of prescribing for specific conditions. ~~The importance of these findings is~~Further research is required on whether ~~such m~~multi-drug ~~therapy~~ prescribing influences the outcomes of care for chronic conditions.

Article summary

Strengths and limitations of this study

- The study was based on large-scale data linking common chronic conditions from general practice populations to prescription data over a 2-year time-period.
- The study highlights the innovative approach to multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug therapy on potentially 'optimal' drug prescribing in populations.
- The study uses a specific but limited number of common chronic conditions to illustrate the approach to linking comorbidity and multi-drug data within a single large region of the UK.
- The study used overall broad measures of drug prescribing and further research is required to understand the specific influence of multi-drug dose and duration on longer-term outcomes.

Introduction

Many older people experience two or more morbidities at the same time, defined as multimorbidity, and within this ~~C~~comorbidity is defined as other co-occurring diseases in the same individual with an index condition,[1,2] ~~, and is~~ These are important concepts as ~~other~~ the experience of multiple conditions at the same time may influence the progression and treatment of ~~the~~ an index condition.[1] Current evidence of the overall implications of chronic diseases, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.[2,3,4,5] Although the health impact of chronic disease comorbidity has been studied, there have been few studies on how chronic diseases comorbidity might influence drug use and related clinical decisions especially in general practice. This is a significant evidence gap despite the fact that drug~~s~~ interventions feature routinely in many disease guidelines. Currently, the model for managing chronic diseases focuses on treating individual conditions, and patients may on the one hand benefit from the drug treatment of each of their chronic conditions; however there is a risk of multiple drug therapy, side effects and drug interactions which could in combination be detrimental.[5,6,7]

Many national health care policies have developed frameworks for chronic disease models of care and specific guidelines for the optimal management of chronic diseases. Examples include policy and guidelines for the common conditions in the general population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways disease and depression.[7,8,9,10,11,12] In addition, these guidelines are beginning to be adapted for the common experience of comorbid conditions, particularly by older people, for each of these individual conditions.[12,13] Since people with one or more chronic conditions are increasing in number, this has increasingly brought in focus the scale and quantity of multiple drug prescribing in general populations. The key questions then become (i) how does multiple drug prescribing relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular disease share aetiology and common drug treatment pathways, but it is still important to understand the scale of multiple drug therapy that might be associated when these conditions co-occur together in the same individual. Many chronic diseases also have conditions which are related to mechanisms other than patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

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depression, and this epidemiology provides the scale of multiple drug therapies when co-occurring conditions might be un-related.

In terms of the current evidence in this field, much of it has focused around 'polypharmacy' studies.[~~13~~14,~~14~~15,~~15~~ 16] However, whilst this might seem an appropriate broad umbrella term, in research and clinical approaches, it has often focused on ~~multiple~~ arbitrarily chosen number of drugs, and linked the term to either inappropriate prescribing or associated adverse ~~associated~~ events in older populations.[16] This lack of consensus defined approach to this problem has led to an argument for less ambiguous terminology[17], and we propose that 'multi-drug' therapy is used to link in with the standard approach to two or more conditions, which is 'multi-morbidity'. Within this evidence, ~~this~~ there is still ~~creates the~~a clear gap ~~of~~ in how ~~multi~~morbidity~~ple conditions~~ link to ~~multi~~drug~~ple drugs~~ prescribing, and whether comorbidity influences the drug ~~optimal~~ prescribing ~~of~~ for an index disease.

In this study, the focus was on six common chronic conditions in the general population, which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of these chronic conditions for the purpose of the study is based on a number of factors including the epidemiology, especially prevalence of the diseases, as well as aetio-pathogenesis and impacts on quality of life and psychological well-being. For example, while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a common pathological basis of causation (the 'vascular group'), and often co-exist in one patient, they are also known to have high mortality rates - hence the drive towards measures aimed at optimising the management of these diseases.[~~16~~18,~~17~~ 19] The other three, non-vascular chronic conditions - ~~Chronic~~ chronic ~~O~~obstructive ~~P~~pulmonary ~~D~~disease (COPD), ~~Osteoarthritis~~ osteoarthritis (OA) and ~~Depression~~ depression are leading causes of morbidity, high cost of care and psychological distress respectively.[~~18,19,~~20,21,22] The rationale for our focus on few selected common conditions was also to provide common comorbidity combinations which are potentially treated with drugs as a key intervention.

In this study, we investigated two separate issues using the selected group of vascular and non-vascular conditions. First, we ~~In addition to~~wanted to investigat~~inge~~ the relative multi~~-ple~~ drug~~s~~ prescribing ~~in comorbidity compared to one of the~~for each of six chosen index examples, comparing comorbid groups with prescribing levels in the respective

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index groups. Second, ~~there was also a~~we wanted to test of whether vascular comorbidity influenced ~~optimal~~ key drug prescribing for chosen conditions. The vascular group were likely to be on similar multiple drugs, so the distinct hypothesis was tested, that was drug prescribing in vascular conditions overall may influence key drug prescribing in the individual non-vascular conditions of COPD, OA or depression.

~~The patients were classified into the individual condition groups, and then two specific study groups were constructed: vascular group (population with at least one of diabetes mellitus, cardiovascular disease or cerebrovascular disease) and non-vascular group of individual conditions (chronic obstructive pulmonary disease, osteoarthritis or depression). The individual groups enabled the comparison of index groups to those with comorbidity. The vascular group were likely to be on similar multiple drugs, so a separate hypothesis was tested, that was prescribing in vascular conditions overall may influence prescribing in the individual non-vascular conditions of chronic obstructive pulmonary disease, osteoarthritis and depression.~~

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Methods

Design and Study population: The cross-sectional study was conducted using two linked databases on patients aged 40 years and over presenting to general practice over a 2-year time period (from 1st January 2002 to 31st December 2003). We wanted to investigate what multi-drug prescribing levels were before a national UK performance-based incentive (Quality outcomes Framework) was implemented to test the associations between comorbidity and routine multi-drug prescribing. Ethical approval for the use of these anonymised databases was granted by the North Staffordshire Research Ethics Committee

Settings: The clinical and prescription databases analysed were derived from an anonymised computer recorded consultations from eleven general practices from the North Staffordshire Keele GP research partnership. The partnership covers a range of practices covering varying socioeconomic groups within rural and urban areas and has been involved in data collection over time for the purpose of epidemiological studies. There is an on-going process of data validation to improve data quality, and there is evidence that this measure improves data recording by general practitioners and their teams.[~~21~~22,23]

Chronic disease data: The Consultation in Primary Care Archive (CiPCA) database focuses on the routinely collected morbidity encounters in actual consultations and coded using a standard clinical classification (Read codes).[22-24] Patients who had a record of a disease-specific READ coded morbidity of interest were included in the study and the main codes were used with all associated "daughter codes". The main READ codes that were used to define the chronic disease groups were: diabetes mellitus (Read codes C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58), excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and depression (E11, E20, Eu and excluding psychosis).

~~**Study groups: definitions**~~

~~The patients were classified into the individual condition groups, and then two specific study groups were constructed: vascular group (population with at least one of diabetes mellitus, cardiovascular disease or cerebrovascular disease) and non-vascular group of individual conditions (chronic obstructive pulmonary disease, osteoarthritis or depression). The individual groups enabled the comparison of index groups to those with comorbidity. The vascular group were likely to be on similar multiple drugs, so a separate hypothesis was tested, that was prescribing in vascular conditions overall may influence prescribing in the individual non-vascular conditions of chronic obstructive pulmonary disease, osteoarthritis and depression.~~

Comorbidity: definitions

There were two approaches to defining comorbidity. First, comorbidity was defined as the presence of one of the other five selected conditions. So using the diabetes population as an example, the diabetes 'index' group was defined as diabetes 'alone' and without anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at least one of the other five conditions. The index 'alone' group would also enable the capture of the other morbidity that was outside of the study selected conditions. This definition was applied to each of the six chronic conditions individually. Second, in the vascular group, comorbidity was defined separately as the individual and specific addition of COPD, OA or depression, and irrespective of whether the latter three occurred together.

~~The approach taken to looking at specific groups and conditions was based on a combination of clinical rationale and feasibility. Whilst, one could have investigated any~~

~~number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the "Vascular" level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be over lapping of drug treatments. However, the "non-vascular" group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group-level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups.~~

~~P~~Prescribed drug measure: overall multi-drug count definitions

The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification.[~~23~~ 25] The BNF consists of 15 main chapters based on the systems of the body, and within which there are further sub-sections for specific clinical indications. Only patients on repeat drug prescriptions were selected for defining measures because this gives a better representation of multiple drugs used on a long term basis for the majority of patients with chronic conditions.

Specific drug treatment chapters for the six chronic diseases of interest in the study were identified and used as a summary of multi-drug counts. The BNF chapter for cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6, and for osteoarthritis under chapters 4 and 10. This means that overall; there were five main BNF chapters, which could constitute a measure of drug counts of up to a total of 5. The multi-drug count definition in this approach would then specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

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~~Prescribed drug measure~~Vascular comorbidity and drug ~~: optimal drug definitions~~prescribing for non-vascular conditions

~~Optimal~~ The key likelihood of receiving drug treatments for the specific conditions of COPD, OA and depression in the study population with vascular comorbidity was also investigated. In this approach the 'vascular' comorbidity was defined as the group any one

of diabetes, cardiovascular disease and cerebrovascular disease. The non-vascular groups were then individually compared with and without vascular comorbidity. For example, the COPD group was compared with vascular comorbidity to the COPD without vascular comorbidity, in relation to the likelihood of receiving COPD-specific drug treatment.

Whilst ~~optimal~~ the key drug treatments ~~of~~ for ~~these conditions~~COPD, OA and depression can be examined in different ways such as the use of specific drugs, or drug doses and duration of drug therapy, we wanted to first establish the simplest likelihood of a patient given any one of ~~an optimal~~the key group of drugs for COPD, OA or depression. The ~~optimal~~ group of drugs derived from guidelines for COPD[10] included bronchodilators, corticosteroids~~,~~, inhaled steroids~~,~~ and oxygen~~mucolytics~~ (BNF sections 3.1, 3.2, 3.5 and 3.6). The ~~optimal~~ group of drugs for ~~osteoarthritis~~[24] osteoarthritis[26] included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The ~~optimal~~ group of drugs for depression[11] included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and 4.3).

Analysis

The first analyses was to describe the 2-year period prevalence of the 5 main BNF chapters in the specified chronic disease population, with a focus on some of the common drugs that were prescribed within each chapter expressed as drug prevalence/10,000 population aged 40 years and over, and differences were assessed using Chi-square tests. The five main chapter drug categories prevalence are described by age, gender and deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD) which is a composite score that is linked to postal address codes.[25-27] The IMD score was categorised into the bottom 20% (most deprived), middle 60% and the top 20% score (most affluent).

For each of the six chronic conditions, associations between the comorbid groups and higher multi-drug counts were compared to the respective reference 'alone' group. The 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and compared to 2 counts or less. Associations using logistic regression were expressed as Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios comparing prevalence of each drug count category in the comorbid group compared to the 'alone' group. Then for the vascular group, associations between each of the comorbid

group with COPD, OA or depression were compared to the vascular 'alone' alone and higher multi-drug counts were then estimated.

Finally, the data was analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD and at least one of the vascular conditions; OA with at least one of the vascular conditions; and depression with at least one of the vascular conditions. Each group was the compared to their respective vascular group e.g. COPD and vascular group compared to COPD without a vascular condition, by the specific optimal drug treatment. Association estimates are presented both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were carried out using SPSS version 17.0 statistical software.

Results

Study population

In the study population of 12,875 aged 40 years and over, the ~~2-year time-period prevalence estimated per 10,000 for~~number of patients prescribed with ~~the~~ cardiovascular system drug~~ss was~~ were 9,384 (2-year time-period prevalence 73%)~~7,289~~, ~~for~~ respiratory system drugs w~~as~~ere 2,861 (22%)~~2,222~~, ~~for~~ non-opioid analgesia ~~was~~ were 5,395 (42%)~~4,190~~, ~~for~~ anti-depressants w~~as~~ere ~~2,517~~3,241 (25%), ~~for~~ anti-diabetic drugs ~~was~~ were 2,916 (~~2,265~~23%) and musculoskeletal system anti-inflammatory drugs ~~was~~ were 2143 ~~1,664~~ (17%) (**Table 1**).

In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% deprivation status were significantly more likely to be prescribed all ~~five~~ main drug categories, except for the cardiovascular system (Chi-square test for trend $p<0.001$). For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were significantly higher for men compared to women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD ($p=0.462$). Prevalence figures were lower for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (Chi square test $p<0.001$ (**Table 2**)).

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Individual chronic condition comorbidity and higher multi-drug counts

For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence numbers were greater for the individual groups without the other five comorbid conditions compared to the numbers for the individual conditions with comorbidity of other five conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone' ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for diabetes comorbid group.

Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

Vascular condition comorbidity and higher multi-drug counts

The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group comorbid with OA OR 3.0 (2.6 to 3.5).

Comorbid vascular conditions and optimal non-vascular condition prescribing

The three specific non-vascular groups of COPD, OA and depression were compared with comorbid vascular conditions to without such vascular comorbidity in terms of their respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation, the association between the COPD and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an Odds Ratio of

0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared to their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).

Discussion

Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years and over with one of six specified and common chronic conditions showed the scale of multi-drug prescribing, which was higher in the presence of comorbidity compared to the respective index groups. Whilst previous evidence has shown the high levels of multiple drug prescribing ~~'polypharmacy'~~[15], our study findings link the disease status, comorbidity status to the measure of multi-drug prescribing.

Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or the non-vascular (COPD, OA or depression), the higher levels of multi-drug prescribing varied. All six conditions with comorbidity compared to their index condition had much higher multi-drug count, even adjusting for age, gender and deprivation. The measure of multi-drug count was notably distinct by the use of five different main drug chapter categories which were for different body systems, which means that this 'outcome' was not about multiple drugs use for the same condition. For example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different and distinct body systems, and not to the different drugs under the same chapter. The chronic condition of depression comorbidity had the strongest strength of association with higher multi-drug counts, followed by cardiovascular disease comorbidity, and the estimates of association for cerebrovascular disease, osteoarthritis and diabetes were similar. These findings suggest that the index condition and comorbidity may influence the range of multi-drug prescribing, and generates the interesting hypothesis on the potential variation in clinical outcomes of the index conditions may be because of underlying comorbid drug prescribing.

The study also grouped the vascular-related conditions to investigate the influence of non-vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of COPD, OA or depression). Again, the adjusted associations were significant, with vascular comorbidity being associated with higher-multi-drug counts compared to the respective 'vascular index' group. Here the clinical implication is that vascular comorbidity in populations aged 40 years and over might not only be associated with multiple vascular drugs as routinely suggested by clinical ~~guidelines[26]~~ guidelines[28], but by a range of

conditions such as comorbidity of COPD, OA or depression. It is possible that these conditions and the drug treatments for them may also in the end influence the health and healthcare outcomes of the index vascular conditions.[27 29]

In terms of the influence of comorbidity on ~~optimal~~ key drug prescribing, our study findings show that vascular comorbidity in COPD and depression is associated with ~~sub-optimal~~ lower likelihood of drug prescribing for the respective conditions of COPD and depression. Similar findings, particularly for sub-optimal depression drug treatment, when depression is comorbid with chronic disease has been shown previously.[28 30, 29-31] However, such findings for osteoarthritis were not found, and here it is possible that the 'outcome' of analgesia was too broad, as analgesia use covers a range of other painful conditions, in addition to osteoarthritis. Although the ~~optimal~~key drug definition was simple and broad, our study findings seem to suggest that comorbidity does influence ~~optimal~~ drug prescribing for specific conditions~~, and further reasons for this might dis-entangle whether it is due to drug therapeutic or diagnostic conflicts~~. Whether this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-disease interactions and the overall well-being of the patient is the important question raised by the findings.

The approach taken to looking at specific groups and six common conditions was based on a combination of clinical rationale and feasibility. Whilst, one could have investigated any number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the "vascular" level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be over-lapping of drug treatments. However, the "non-vascular" group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group-level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups. The study focus was also on comorbidity and further research is also required on how multimorbidity, defined as two or more conditions, influences the overall prescribing of multiple drugs and when the unit of analysis for outcome is not the disease but the arguably more important patient-centred outcomes.

The large scale study of specified chronic diseases was conducted using an anonymised database for a 2-year time-period. In terms of the cross-sectional associations, the findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer

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clinical implications as outlined earlier. However, the implications of the associations between comorbidity and optimal drug definitions may be limited in this cross-sectional design and these may be treated cautiously as emergent findings. The chronic disease definitions were also based on routinely collected registers from general practices, which were and are part of a research network dedicated to the collection of clinical data in actual consultation. Whilst these chronic disease registers may be subject to variations in ~~recording~~[30] recording[32], the study analyses provide the estimates of association in actual clinical practice across 11 different sites.

The drug definitions were based on routinely coded repeat prescriptions and over a 2-year time-period represent an appropriate measure at the simpler but distinct broad system category.- Patients however will also have been prescribed other drug categories outside of the five main categories that we had selected and for other less common conditions from the ones selected in the study, which means these drug levels are a specific estimate. The construction of our study defined index or 'alone' groups (without the other 5 conditions) provided the relative multi-drug level estimates to when the index condition was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone' group provide an estimate of main drug system prescribing without the associated condition (i.e. for other indications) compared to levels when there is a clear comorbidity record. However, this is time-defined by a 2-year time window, so some mis-classification may be possible and further research could explore how broad system drug definitions capture the underlying and specific common diagnostic categories. Further research is also required for the arguably more complex assimilation of the range of defined drug categories, other multi-morbidity and to investigate specific effect of individual drugs categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not available over the counter and are usually clinician prescribed. So it is possible that common over the counter drugs, particularly in relation to osteoarthritis, may be an under-estimate; however, the selection of repeated prescribing would mitigate against such under-estimation. Finally, although a large scale study, these general practices are drawn from one region of England, and whilst this might limit generalisability, the internal validity of the findings still remains.

In conclusion, our study findings show the links between common chronic conditions, comorbidity and associated multi-drug prescribing. The key and distinct finding is that the study shows that multi-drug prescribing defined by a range of selected but different systems is high in chronic conditions and higher in comorbidity. The common group of vascular conditions are not the only ones associated with their 'own' guideline driven multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and

depression adds to the multi-drugs burden in patients. The importance of these findings, in addition to quantifying the scale, is whether such multi-drug therapy influences the quality of care for each of the individual conditions. Our findings suggest the potential for sub-optimal drug treatment as a consequence is in line with other ~~evidence[34]~~ evidence[33], but further research is required to investigate the impact of disease status, comorbidity, multi-drug therapy on prospective and long-term outcomes of clinical care.

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Contributorship statement: ER and DG coordinated the study data collection and contributed to the writing of the manuscript. ER, DG and UTK were involved in study design and developed the statistical approaches. UTK conceived and designed the study, was involved with analysis, interpretation and contributed to the writing of this manuscript. All authors have contributed and approved the final version of this manuscript.

Competing interests: There are no competing requests.

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Data sharing: Data is not available for sharing under existing governance arrangements and no additional data is available.

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Table 1: Prescribed drug prevalence by BNF main chapter and specific sections

BNF Chapter	BNF subsections	BNF Classification	Drug examples	Number	Drug prevalence/ 10,000[†]
2 Cardiovascular system				9384	7289
	2.9	Antiplatelet drugs	Aspirin, Clopidogrel Dipyridamole	*5044*	*3918*
	2.8	Anticoagulants	Warfarin	*669*	*520*
	2.2	Diuretics	Thiazide diuretics	*4912*	*3815*
	2.4	Beta blockers	Bisoprolol	*4034*	*3133*
	2.5	*ACE Inhibitors or *ARB	Ramipril, candesartan	*4250*	*3301*
	2.6	Nitrates, Calcium antagonists	GTN, Amlodipine	*4984*	*3817*
	2.12	Lipid regulating drugs	Simvastatin	*4894*	*3801*
3 Respiratory system				*2861*	2222
	3.1	Bronchodilators	Salbutamol	*2775*	*2155*
	3.2	Corticosteroids	Beclomethasone	*2140*	*1662*
	~~3.5~~	~~Respiratory stimulants~~	~~Doxapram~~	~~*0*~~	~~0~~
	3.6	Oxygen	n/a	*94*	73
4 Central nervous system drugs				*7478*	5808
	4.7.1	Non-Opioid analgesics	Paracetamol	*5395*	*4190*
	4.7.2	Opioid analgesics	Codeine,Tramadol	*855*	*664*
	4.1	Hypnotics and anxiolytics	Diazepam	*1180*	917
	4.3	Selective Serotonin Reuptake Inhibitors Tricyclic Antidepressants	Fluoxetine, Citalopram, Amitriptyline	*3241*	2517

6 Endocrine system				*2916*	2265
	6.1.1	Insulin	Insulin, Humalog	*632*	*491*
	6.1.2	Oral anti-diabetic drugs	Metformin, Gliclazide	*2334*	*1805*
10 Musculoskeletal and joint disease				*2143*	1664
	10.1.1	Non-steroidal anti-inflammatory drugs	Ibuprofen, cyclooxygenase inhibitors	*2143*	*1664*

[†]*Population refers to those with one of six chronic conditions (n* = 12875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF)

Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	Musculo-skeletal System
Age (years)						
40-54	2738	1257 (46)	441 (16)	1447 (53)	555 (20)	378 (14)
55-69	4963	3712 (75)	1131 (23)	2694 (54)	1250 (25)	1003 (20)
70-84	4459	3807 (85)	1154 (26)	2824 (63)	1010 (23)	703 (16)
85 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
Gender						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
Deprivation**						
Deprived status	2609	1952 (75)	780 (30)	1705 (65)	695 (27)	474 (18)
Middle status	7228	5308 (73)	1538 (21)	4184 (58)	1616 (22)	1223 (17)
Affluent status	2203	1584 (72)	354 (16)	1185 (54)	419 (19)	377 (17)

***Deprivation measured by Index of Multiple of Deprivation, figures in brackets refer to the percentage of each study factor sub-group*

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted
	0	1	2	3	4	5	Odds Ratio (95% CI)
Diabetes 'alone'	239	1178	4332	3120	1021	110	1.0
Diabetes comorbidity	58	492	2208	4523	2353	366	3.50 (3.0-4.2)
Prevalence ratio	*0.2*	*0.4*	*0.5*	*1.5*	*2.3*	*3.3*	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
Prevalence ratio	*0.2*	*0.3*	*0.9*	*2.6*	*8.3*	*7.6*	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
Prevalence ratio	*0.1*	*0.4*	*1.1*	*2.5*	*9.7*	*n/a*	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
Prevalence ratio	*0.20*	*0.4*	*0.8*	*1.5*	*5.00*	*n/a*	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
Prevalence ratio	*0.1*	*0.5*	*1.0*	*1.8*	*5.2*	*54*	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
Prevalence ratio	*0.17*	*0.34*	*1.15*	*4.58*	*13.7*	*n/a*	

**Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, **Comorbid drug ratio = 2-year drug count prevalence in the comorbid group/2-year drug count prevalence in the disease alone group; adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease*

Table 4: Associations between vascular comorbidity groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted
	0	1	2	3	4	5	Odds Ratio (95% CI)
Vascular group only*	199	2373	4018	2547	773	89	1.0
Vascular group and COPD	85	677	2854	4207	2008	169	4.63 (3.8-5.7)
Prevalence ratio	*0.43*	*0.29*	*0.71*	*1.65*	*2.60*	*1.90*	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
Prevalence ratio	*0.15*	*0.37*	*0.87*	*1.45*	*2.01*	*3.92*	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
Prevalence ratio	*0.35*	*0.35*	*0.93*	*1.54*	*1.76*	*1.03*	

**Vascular group only is the reference group without COPD, OA or depression; prevalence ratio is comparing vascular comorbid group with vascular group alone for each drug count category, adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less)*

Table 5: ~~Optimal~~ Key drug treatment of non-vascular conditions in vascular comorbidity

Numbers (%)	~~Optimal~~ Key drug treatments		Unadjusted	Adjusted
	No	Yes	Odds Ratio (95% CI)	Odds Ratio (95% CI)
COPD without vascular comorbidity	123 (22)	937 (88)	1.0	1.0
COPD and vascular comorbidity	87 (19)	382 (81)	0.58 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

***~~Optimal d~~Drug treatment for COPD, OA or depression respectively, adjusted for age, gender and deprivation as measured by Index of Multiple deprivation*

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~~1.~~

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Title: Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Abstract

Objectives: The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition key drug prescribing.

Design: Cross-sectional study linking anonymised computer consultations with prescription records for a 2-year time-period.

Setting: 11 general practices in North Staffordshire, England.

Participants: Study groups aged 40 years and over (N=12,875). Within six conditions, comorbid group with the other 5 conditions was compared to an 'alone' group without them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and cerebrovascular disease) comorbidity influenced COPD, OA or depression drug prescribing was investigated.

Outcome Measures: Based on the British National Formulary, five main drug chapters constituted a measure of drug counts, with low count as 2 or less and high multi-drug count as 3 or more. Key drugs prescribed for COPD, OA and depression were derived from guidelines.

Results: The adjusted associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in key COPD drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In depression, vascular comorbidity was associated with a reduction in key depression drug treatments (OR 0.6 (0.4 to 0.7)).

Conclusions: Our findings show multi-drug prescribing for different body systems is higher with comorbidity and may be associated with lower likelihood of prescribing for specific conditions. Further research is required on whether multi-drug prescribing influences the outcomes of care for chronic conditions.

Article summary

Strengths and limitations of this study

- The study was based on large-scale data linking common chronic conditions from general practice populations to prescription data over a 2-year time-period.
- The study highlights the innovative approach to multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug therapy on potentially 'optimal' drug prescribing in populations.
- The study uses a specific but limited number of common chronic conditions to illustrate the approach to linking comorbidity and multi-drug data within a single large region of the UK.
- The study used overall broad measures of drug prescribing and further research is required to understand the specific influence of multi-drug dose and duration on longer-term outcomes.

Introduction

Many older people experience two or more morbidities at the same time which is defined as multimorbidity, and within this comorbidity is defined as other co-occurring diseases in the same individual with an index condition.[1,2] These are important concepts as the experience of multiple conditions at the same time may influence the progression and treatment of an index condition. Current evidence of the overall implications of chronic diseases, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.[3,4,5] Although the health impact of chronic disease comorbidity has been studied, there have been few studies on how chronic diseases comorbidity might influence drug use and related clinical decisions especially in general practice. This is a significant evidence gap despite the fact that drug interventions feature routinely in many disease guidelines. Currently, the model for managing chronic diseases focuses on treating individual conditions, and patients may on the one hand benefit from the drug treatment of each of their chronic conditions; however there is a risk of multiple drug therapy, side effects and drug interactions which could in combination be detrimental.[6,7]

Many national health care policies have developed frameworks for chronic disease models of care and specific guidelines for the optimal management of chronic diseases. Examples include policy and guidelines for the common conditions in the general population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways disease and depression.[8,9,10,11,12] In addition, these guidelines are beginning to be adapted for the common experience of comorbid conditions, particularly by older people, for each of these individual conditions.[13] Since people with one or more chronic conditions are increasing in number, this has increasingly brought in focus the scale and quantity of multiple drug prescribing in general populations. The key questions then become (i) how does multiple drug prescribing for different systems relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular disease share aetiology and common drug treatment pathways, but it is still important to understand the scale of multiple drug therapy that might be associated when these conditions co-occur together in the same individual. Many chronic diseases also have conditions which are related to mechanisms other than patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

depression, and this epidemiology provides the scale of multiple drug therapies when co-occurring conditions might be un-related.

In terms of the current evidence in this field, much of it has focused around 'polypharmacy' studies.[14,15,16] However, whilst this might seem an appropriate broad umbrella term, in research and clinical approaches, it has often focused on arbitrarily chosen number of drugs, and linked the term to either inappropriate prescribing or associated adverse events in older populations.[16] This lack of consensus defined approach to this problem has led to an argument for less ambiguous terminology[17], and we propose that 'multi-drug' therapy is used to link in with the standard approach to two or more conditions, which is 'multi-morbidity'. Within this evidence, there is still a clear gap in how morbidity link to drug prescribing, and whether comorbidity influences the drug prescribing for an index disease.

In this study, the focus was on six common chronic conditions in the general population, which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of these chronic conditions for the purpose of the study was based on a number of factors including the epidemiology, especially prevalence of the diseases, as well as aetio-pathogenesis and impacts on quality of life and psychological well-being. For example, while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a common pathological basis of causation (the 'vascular group'), and often co-exist in one patient, they are also known to have high mortality rates - hence the drive towards measures aimed at optimising the management of these diseases.[18,19] The other three, non-vascular chronic conditions - chronic obstructive pulmonary disease (COPD), osteoarthritis (OA) and depression are leading causes of morbidity, high cost of care and psychological distress respectively. [20,21,22] The rationale for our focus on few selected common conditions was also to provide common comorbidity combinations which are potentially treated with drugs as a key intervention.

We investigated two separate issues using the selected group of vascular and non-vascular conditions. First, we wanted to investigate the relative multi-drug prescribing for each of six chosen index examples, comparing comorbid groups with prescribing levels in the respective index groups. Second, we wanted to test whether vascular comorbidity influenced key drug prescribing for chosen conditions. The vascular group were likely to be on similar multiple drugs, so the distinct hypothesis was tested, that was drug

prescribing in vascular conditions overall may influence key drug prescribing in the individual non-vascular conditions of COPD, OA or depression.

Methods

Design and Study population: The cross-sectional study was conducted using two linked databases on patients aged 40 years and over presenting to general practice over a 2-year time period (from 1st January 2002 to 31st December 2003). We wanted to investigate what multi-drug prescribing levels were before a national UK performance-based incentive (Quality outcomes Framework) was implemented to test the associations between comorbidity and routine multi-drug prescribing. Ethical approval for the use of these anonymised databases was granted by the North Staffordshire Research Ethics Committee

Settings: The clinical and prescription databases analysed were derived from an anonymised computer recorded consultations from eleven general practices from the North Staffordshire Keele GP research partnership. The partnership covers a range of practices covering varying socioeconomic groups within rural and urban areas and has been involved in data collection over time for the purpose of epidemiological studies. There is an on-going process of data validation to improve data quality, and there is evidence that this measure improves data recording by general practitioners and their teams.[23]

Chronic disease data: The Consultation in Primary Care Archive (CiPCA) database focuses on the routinely collected morbidity encounters in actual consultations and coded using a standard clinical classification (Read codes).[24] Patients who had a record of a disease-specific READ coded morbidity of interest were included in the study and the main codes were used with all associated "daughter codes". The main READ codes that were used to define the chronic disease groups were: diabetes mellitus (Read codes C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58), excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and depression (E11, E20, Eu and excluding psychosis).

Comorbidity: definitions

There were two approaches to defining comorbidity. First, comorbidity was defined as the presence of one of the other five selected conditions. So using the diabetes population as

an example, the diabetes 'index' group was defined as diabetes 'alone' and without anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at least one of the other five conditions. The index 'alone' group would also enable the capture of the other morbidity that was outside of the ones within the study. This definition was applied to each of the six chronic conditions individually. Second, in the vascular group, comorbidity was defined separately as the individual and specific addition of COPD, OA or depression, and irrespective of whether the latter three occurred together.

Prescribed drug measure: overall multi-drug count definitions

The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification.[25] The BNF consists of 15 main chapters based on the systems of the body, and within which there are further sub-sections for specific clinical indications. Only patients on repeat drug prescriptions were selected for defining measures because this gives a better representation of multiple drugs used on a long term basis for the majority of patients with chronic conditions.

Specific drug treatment chapters for the six chronic diseases of interest in the study were identified and used as a summary of multi-drug counts. The BNF chapter for cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6, and for osteoarthritis under chapters 4 and 10. This means that overall; there were five main BNF chapters, which could constitute a measure of drug counts of up to a total of 5. The multi-drug count definition in this approach would then specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

Vascular comorbidity and drug prescribing for non-vascular conditions

The key likelihood of receiving drug treatments for the specific conditions of COPD, OA and depression in the study population with vascular comorbidity was also investigated. In this approach the 'vascular' comorbidity was defined as the group any one of diabetes, cardiovascular disease and cerebrovascular disease. The non-vascular groups were then individually compared with and without vascular comorbidity. For example, the COPD group was compared with vascular comorbidity to the COPD without vascular comorbidity, in relation to the likelihood of receiving COPD-specific drug treatment.

Whilst the key drug treatments for COPD, OA and depression can be examined in different ways such as the use of specific drugs, or drug doses and duration of drug therapy, we wanted to first establish the simplest likelihood of a patient given any one of the key group of drugs for COPD, OA or depression. The group of drugs derived from guidelines for COPD[10] included bronchodilators, corticosteroids, inhaled steroids and oxygen(BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for osteoarthritis[26] included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for depression[11] included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and 4.3).

Analysis

The first analyses was to describe the 2-year period prevalence of the 5 main BNF chapters in the specified chronic disease population, with a focus on some of the common drugs that were prescribed within each chapter expressed as drug prevalence/10,000 population aged 40 years and over, and differences were assessed using Chi-square tests. The five main chapter drug categories prevalence are described by age, gender and deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD) which is a composite score that is linked to postal address codes.[27] The IMD score was categorised into the bottom 20% (most deprived), middle 60% and the top 20% score (most affluent).

For each of the six chronic conditions, associations between the comorbid groups and higher multi-drug counts were compared to the respective reference 'alone' group. The 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and compared to 2 counts or less. Associations using logistic regression were expressed as Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios comparing prevalence of each drug count category in the comorbid group compared to the 'alone' group. Then for the vascular group, associations between each of the comorbid group with COPD, OA or depression were compared to the vascular 'alone' alone and higher multi-drug counts were then estimated.

Finally, the data was analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD and at least one of the vascular conditions; OA with at least one of the vascular conditions; and depression with at least one of the vascular conditions. Each group was the compared to their respective

vascular group e.g. COPD and vascular group compared to COPD without a vascular condition, by the specific optimal drug treatment. Association estimates using logistic regression are presented both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were carried out using SPSS version 17.0 statistical software.

Results

Study population

In the study population of 12,875 aged 40 years and over, the number of patients prescribed with cardiovascular system drugs were 9,384 (2-year time-period prevalence 73%), respiratory system drugs were 2,861 (22%), non-opioid analgesia were 5,395 (42%), anti-depressants were 3,241 (25%), anti-diabetic drugs were 2,916 (23%) and musculoskeletal system anti-inflammatory drugs were 2143 (17%) (**Table 1**).

In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% most deprived status were significantly more likely to be prescribed all main drug categories, except for the cardiovascular system (Chi-square test for trend $p<0.001$). For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were significantly higher for men compared to women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD ($p=0.462$). Prevalence figures were lower for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (Chi square test $p<0.001$ (**Table 2**)).

Individual chronic condition comorbidity and higher multi-drug counts

For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence numbers were greater for the individual groups without the other five comorbid conditions compared to the numbers for the individual conditions with comorbidity of other five conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone' ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for diabetes comorbid group.

Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group ordered by

strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

Vascular condition comorbidity and higher multi-drug counts

The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group comorbid with OA OR 3.0 (2.6 to 3.5).

Comorbid vascular conditions and optimal non-vascular condition prescribing

The three specific non-vascular groups of COPD, OA and depression were compared with comorbid vascular conditions to without such vascular comorbidity in terms of their respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation, the association between the COPD and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared to their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).

Discussion

Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years and over with one of six specified and common chronic conditions showed the scale of multi-drug prescribing, which was higher in the presence of comorbidity compared to the respective index groups. Whilst previous evidence has shown the high levels of multiple

drug prescribing[15], our study findings link the disease status, comorbidity status to the measure of multi-drug prescribing for different systems.

Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or non-vascular (COPD, OA or depression), the higher levels of multi-drug prescribing varied. All six conditions with comorbidity compared to their index condition had much higher multi-drug count, even adjusting for age, gender and deprivation. The measure of multi-drug count was notably distinct by the use of five different main drug chapter categories which were for different body systems, which means that this 'outcome' was not about multiple drugs use for the same condition. For example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different and distinct body systems, and not to the different drugs under the same chapter. The chronic condition of depression comorbidity had the strongest strength of association with higher multi-drug counts, followed by cardiovascular disease comorbidity, and the estimates of association for cerebrovascular disease, osteoarthritis and diabetes were similar. These findings suggest that the index condition and comorbidity may influence the range of multi-drug prescribing, and generates the interesting hypothesis on the potential variation in clinical outcomes of the index conditions may be because of underlying comorbid drug prescribing.

The study also grouped the vascular-related conditions to investigate the influence of non-vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of COPD, OA or depression). Again, the adjusted associations were significant, with vascular comorbidity being associated with higher-multi-drug counts compared to the respective 'vascular index' group. Here the clinical implication is that vascular comorbidity in populations aged 40 years and over might not only be associated with multiple vascular drugs as routinely suggested by clinical guidelines[28], but by a range of conditions such as comorbidity of COPD, OA or depression. It is possible that these conditions and the drug treatments for them may also in the end influence the health and healthcare outcomes of the index vascular conditions.[29]

In terms of the influence of comorbidity on key drug prescribing, our study findings show that vascular comorbidity in COPD and depression is associated with lower likelihood of drug prescribing for the respective conditions of COPD and depression. Similar findings, particularly for sub-optimal depression drug treatment, when depression is comorbid with chronic disease have been shown previously.[30,31] However, such findings for osteoarthritis were not found, and here it is possible that the study definition of analgesia was too broad, as analgesia use covers a range of other painful conditions, in addition to osteoarthritis.

Although the key drug definition was simple and broad, our study findings seem to

suggest that comorbidity does influence drug prescribing for specific conditions. Whether this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-disease interactions and the overall well-being of the patient is the important question raised by the findings.

The approach taken to looking at specific groups and six common conditions was based on a combination of clinical rationale and feasibility. Whilst, one could have investigated any number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the "vascular" level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be over-lapping of drug treatments. However, the "non-vascular" group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group-level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups. The study focus was also on comorbidity and further research is also required on how multimorbidity, defined as two or more conditions, influences the overall prescribing of multiple drugs and when the unit of analysis for outcome is not the disease but the arguably more important patient-centred outcomes.

The large scale study of specified chronic diseases was conducted using an anonymised database for a 2-year time-period. In terms of the cross-sectional associations, the findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer clinical implications as outlined earlier. However, the implications of the associations between comorbidity and the key drug definitions may be limited in this cross-sectional design and these may be treated cautiously as emergent findings. The chronic disease definitions were also based on routinely collected registers from general practices, which were and are part of a research network dedicated to the collection of clinical data in actual consultation. Whilst these chronic disease registers may be subject to variations in recording[32], the study analyses provide the estimates of association in actual clinical practice across 11 different sites.

The drug definitions were based on routinely coded repeat prescriptions and over a 2-year time-period represent an appropriate measure at the simpler but distinct broad system category. Patients however will also have been prescribed other drug categories outside of the five main categories that we had selected and for other less common conditions from the ones selected in the study, which means these drug levels are a specific estimate. The construction of our study defined index or 'alone' groups (without the other

5 conditions) provided the relative multi-drug level estimates to when the index condition was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone' group provide an estimate of main drug system prescribing without the associated condition (i.e. for other indications) compared to levels when there is a clear comorbidity record. However, this is time-defined by a 2-year time window, so some mis-classification may be possible and further research could explore how broad system drug definitions capture the underlying and specific common diagnostic categories. Further research is also required for the arguably more complex assimilation of the range of defined drug categories, other multi-morbidity and to investigate specific effect of individual drugs categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not available over the counter and are usually clinician prescribed. So it is possible that common over the counter drugs, particularly in relation to osteoarthritis, may be an under-estimate; however, the selection of repeated prescribing would mitigate against such under-estimation. Finally, although a large scale study, these general practices are drawn from one region of England, and whilst this might limit generalisability, the internal validity of the findings still remains.

In conclusion, our study findings show the links between common chronic conditions, comorbidity and associated multi-drug prescribing. The key and distinct finding is that the study shows that multi-drug prescribing defined by a range of selected but different systems is high in chronic conditions and higher in comorbidity. The common group of vascular conditions are not the only ones associated with their 'own' guideline driven multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and depression adds to the multi-drugs burden in patients. The importance of these findings, in addition to quantifying the scale, is whether such multi-drug therapy influences the quality of care for each of the individual conditions. Our findings suggest the potential for sub-optimal drug treatment as a consequence is in line with other evidence[33], but further research is required to investigate the impact of disease status, comorbidity, multi-drug therapy on prospective and long-term outcomes of clinical care.

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Table 1: Prescribed drug prevalence by BNF main chapter and specific sections

BNF Chapter	BNF subsections	BNF Classification	Drug examples	Number	Drug prevalence/ 10,000†
2 Cardiovascular system				9384	7289
	2.9	Antiplatelet drugs	Aspirin, Clopidogrel Dipyridamole	*5044*	*3918*
	2.8	Anticoagulants	Warfarin	*669*	*520*
	2.2	Diuretics	Thiazide diuretics	*4912*	*3815*
	2.4	Beta blockers	Bisoprolol	*4034*	*3133*
	2.5	*ACE Inhibitors or *ARB	Ramipril, candesartan	*4250*	*3301*
	2.6	Nitrates, Calcium antagonists	GTN, Amlodipine	*4984*	*3817*
	2.12	Lipid regulating drugs	Simvastatin	*4894*	*3801*
3 Respiratory system				*2861*	2222
	3.1	Bronchodilators	Salbutamol	*2775*	*2155*
	3.2	Corticosteroids	Beclomethasone	*2140*	*1662*
	3.6	Oxygen	n/a	*94*	73
4 Central nervous system drugs				*7478*	5808
	4.7.1	Non-Opioid analgesics	Paracetamol	*5395*	*4190*
	4.7.2	Opioid analgesics	Codeine,Tramadol	*855*	*664*
	4.1	Hypnotics and anxiolytics	Diazepam	*1180*	917
	4.3	Selective Serotonin Reuptake Inhibitors Tricyclic Antidepressants	Fluoxetine, Citalopram, Amitriptyline	*3241*	2517
6 Endocrine system				*2916*	2265
	6.1.1	Insulin	Insulin, Humalog	*632*	*491*
	6.1.2	Oral anti-diabetic drugs	Metformin, Gliclazide	*2334*	*1805*

10 Musculoskeletal and joint disease				*2143*	1664
	10.1.1	Non-steroidal anti-inflammatory drugs	Ibuprofen, cyclooxygenase inhibitors	*2143*	*1664*

†*Population refers to those with one of six chronic conditions (n* = 12875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF) classification

Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	Musculo-skeletal System
Age (years)						
40-54	2738	1257 (46)	441 (16)	1447 (53)	555 (20)	378 (14)
55-69	4963	3712 (75)	1131 (23)	2694 (54)	1250 (25)	1003 (20)
70-84	4459	3807 (85)	1154 (26)	2824 (63)	1010 (23)	703 (16)
85 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
Gender						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
Deprivation**						
Deprived status	2609	1952 (75)	780 (30)	1705 (65)	695 (27)	474 (18)
Middle status	7228	5308 (73)	1538 (21)	4184 (58)	1616 (22)	1223 (17)
Affluent status	2203	1584 (72)	354 (16)	1185 (54)	419 (19)	377 (17)

***Deprivation measured by Index of Multiple of Deprivation, figures in brackets refer to the percentage of each study factor sub-group*

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Diabetes 'alone'	239	1178	4332	3120	1021	110	1.0
Diabetes comorbidity	58	492	2208	4523	2353	366	3.50 (3.0-4.2)
Prevalence ratio	*0.2*	*0.4*	*0.5*	*1.5*	*2.3*	*3.3*	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
Prevalence ratio	*0.2*	*0.3*	*0.9*	*2.6*	*8.3*	*7.6*	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
Prevalence ratio	*0.1*	*0.4*	*1.1*	*2.5*	*9.7*	*n/a*	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
Prevalence ratio	*0.20*	*0.4*	*0.8*	*1.5*	*5.00*	*n/a*	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
Prevalence ratio	*0.1*	*0.5*	*1.0*	*1.8*	*5.2*	*54*	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
Prevalence ratio	*0.17*	*0.34*	*1.15*	*4.58*	*13.7*	*n/a*	

**Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, **Comorbid drug ratio = 2-year drug count prevalence in the comorbid group/2-year drug count prevalence in the disease alone group; adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease*

Table 4: Associations between vascular comorbidity groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Vascular group only*	199	2373	4018	2547	773	89	1.0
Vascular group and COPD	85	677	2854	4207	2008	169	4.63 (3.8-5.7)
Prevalence ratio	*0.43*	*0.29*	*0.71*	*1.65*	*2.60*	*1.90*	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
Prevalence ratio	*0.15*	*0.37*	*0.87*	*1.45*	*2.01*	*3.92*	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
Prevalence ratio	*0.35*	*0.35*	*0.93*	*1.54*	*1.76*	*1.03*	

**Vascular group only is the reference group without COPD, OA or depression; prevalence ratio is comparing vascular comorbid group with vascular group alone for each drug count category, adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less)*

Table 5: Key drug treatment of non-vascular conditions in vascular comorbidity

Numbers (%)	Key drug treatments		Unadjusted	Adjusted
	No	Yes	Odds Ratio (95% CI)	Odds Ratio (95% CI)
COPD without vascular comorbidity	123 (22)	937 (88)	1.0	1.0
COPD and vascular comorbidity	87 (19)	382 (81)	0.58 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

***Drug treatment for COPD, OA or depression respectively, adjusted for age, gender and deprivation as measured by Index of Multiple deprivation*

Title: Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study

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Abstract

Objectives: The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition ~~optimal~~ key drug prescribing.

Design: Cross-sectional study linking anonymised computer consultations with prescription records for a 2-year time-period.

Setting: 11 general practices in North Staffordshire, England.

Participants: Study groups aged 40 years and over (N=12,875). Within six conditions, comorbid group with the other 5 conditions was compared to an 'alone' group without them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and cerebrovascular disease) comorbidity influenced COPD, OA or depression drug prescribing was investigated.

Outcome Measures: Based on the British National Formulary, five main drug chapters constituted a measure of drug counts, with low count as 2 or less and high multi-drug count as 3 or more. Key drugs prescribed for COPD, OA and depression were derived from guidelines.

Results: The adjusted associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in key COPD drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In depression, vascular comorbidity was associated with a reduction in key depression drug treatments (OR 0.6 (0.4 to 0.7)).

Conclusions: Our findings show multi-drug prescribing for different body systems is higher with comorbidity and may be associated with lower likelihood of prescribing for specific conditions. Further research is required on whether multi-drug prescribing influences the outcomes of care for chronic conditions.

Article summary

Strengths and limitations of this study

- The study was based on large-scale data linking common chronic conditions from general practice populations to prescription data over a 2-year time-period.
- The study highlights the innovative approach to multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug therapy on potentially 'optimal' drug prescribing in populations.
- The study uses a specific but limited number of common chronic conditions to illustrate the approach to linking comorbidity and multi-drug data within a single large region of the UK.
- The study used overall broad measures of drug prescribing and further research is required to understand the specific influence of multi-drug dose and duration on longer-term outcomes.

Introduction

Many older people experience two or more morbidities at the same time which is defined as multimorbidity, and within this comorbidity is defined as other co-occurring diseases in the same individual with an index condition.[1,2] These are important concepts as the experience of multiple conditions at the same time may influence the progression and treatment of an index condition. Current evidence of the overall implications of chronic diseases, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.[3,4,5] Although the health impact of chronic disease comorbidity has been studied, there have been few studies on how chronic diseases comorbidity might influence drug use and related clinical decisions especially in general practice. This is a significant evidence gap despite the fact that drug interventions feature routinely in many disease guidelines. Currently, the model for managing chronic diseases focuses on treating individual conditions, and patients may on the one hand benefit from the drug treatment of each of their chronic conditions; however there is a risk of multiple drug therapy, side effects and drug interactions which could in combination be detrimental.[6,7]

Many national health care policies have developed frameworks for chronic disease models of care and specific guidelines for the optimal management of chronic diseases. Examples include policy and guidelines for the common conditions in the general population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways disease and depression.[8,9,10,11,12] In addition, these guidelines are beginning to be adapted for the common experience of comorbid conditions, particularly by older people, for each of these individual conditions.[13] Since people with one or more chronic conditions are increasing in number, this has increasingly brought in focus the scale and quantity of multiple drug prescribing in general populations. The key questions then become (i) how does multiple drug prescribing for different systems relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular disease share aetiology and common drug treatment pathways, but it is still important to understand the scale of multiple drug therapy that might be associated when these conditions co-occur together in the same individual. Many chronic diseases also have conditions which are related to mechanisms other than patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

depression, and this epidemiology provides the scale of multiple drug therapies when co-occurring conditions might be un-related.

In terms of the current evidence in this field, much of it has focused around 'polypharmacy' studies.[14,15,16] However, whilst this might seem an appropriate broad umbrella term, in research and clinical approaches, it has often focused on arbitrarily chosen number of drugs, and linked the term to either inappropriate prescribing or associated adverse events in older populations.[16] This lack of consensus defined approach to this problem has led to an argument for less ambiguous terminology[17], and we propose that 'multi-drug' therapy is used to link in with the standard approach to two or more conditions, which is 'multi-morbidity'. Within this evidence, there is still a clear gap in how morbidity link to drug prescribing, and whether comorbidity influences the drug prescribing for an index disease.

In this study, the focus was on six common chronic conditions in the general population, which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of these chronic conditions for the purpose of the study was based on a number of factors including the epidemiology, especially prevalence of the diseases, as well as aetio-pathogenesis and impacts on quality of life and psychological well-being. For example, while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a common pathological basis of causation (the 'vascular group'), and often co-exist in one patient, they are also known to have high mortality rates - hence the drive towards measures aimed at optimising the management of these diseases.[18,19] The other three, non-vascular chronic conditions - chronic obstructive pulmonary disease (COPD), osteoarthritis (OA) and depression are leading causes of morbidity, high cost of care and psychological distress respectively. [20,21,22] The rationale for our focus on few selected common conditions was also to provide common comorbidity combinations which are potentially treated with drugs as a key intervention.

We investigated two separate issues using the selected group of vascular and non-vascular conditions. First, we wanted to investigate the relative multi-drug prescribing for each of six chosen index examples, comparing comorbid groups with prescribing levels in the respective index groups. Second, we wanted to test ~~of~~ whether vascular comorbidity influenced key drug prescribing for chosen conditions. The vascular group were likely to be on similar multiple drugs, so the distinct hypothesis was tested, that was drug

prescribing in vascular conditions overall may influence key drug prescribing in the individual non-vascular conditions of COPD, OA or depression.

Methods

Design and Study population: The cross-sectional study was conducted using two linked databases on patients aged 40 years and over presenting to general practice over a 2-year time period (from 1st January 2002 to 31st December 2003). We wanted to investigate what multi-drug prescribing levels were before a national UK performance-based incentive (Quality outcomes Framework) was implemented to test the associations between comorbidity and routine multi-drug prescribing. Ethical approval for the use of these anonymised databases was granted by the North Staffordshire Research Ethics Committee

Settings: The clinical and prescription databases analysed were derived from an anonymised computer recorded consultations from eleven general practices from the North Staffordshire Keele GP research partnership. The partnership covers a range of practices covering varying socioeconomic groups within rural and urban areas and has been involved in data collection over time for the purpose of epidemiological studies. There is an on-going process of data validation to improve data quality, and there is evidence that this measure improves data recording by general practitioners and their teams.[23]

Chronic disease data: The Consultation in Primary Care Archive (CiPCA) database focuses on the routinely collected morbidity encounters in actual consultations and coded using a standard clinical classification (Read codes).[24] Patients who had a record of a disease-specific READ coded morbidity of interest were included in the study and the main codes were used with all associated "daughter codes". The main READ codes that were used to define the chronic disease groups were: diabetes mellitus (Read codes C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58), excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and depression (E11, E20, Eu and excluding psychosis).

Comorbidity: definitions

There were two approaches to defining comorbidity. First, comorbidity was defined as the presence of one of the other five selected conditions. So using the diabetes population as

an example, the diabetes 'index' group was defined as diabetes 'alone' and without anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at least one of the other five conditions. The index 'alone' group would also enable the capture of the other morbidity that was outside of the ~~study selected conditions~~ones within the study. This definition was applied to each of the six chronic conditions individually. Second, in the vascular group, comorbidity was defined separately as the individual and specific addition of COPD, OA or depression, and irrespective of whether the latter three occurred together.

Prescribed drug measure: overall multi-drug count definitions

The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification.[25] The BNF consists of 15 main chapters based on the systems of the body, and within which there are further sub-sections for specific clinical indications. Only patients on repeat drug prescriptions were selected for defining measures because this gives a better representation of multiple drugs used on a long term basis for the majority of patients with chronic conditions.

Specific drug treatment chapters for the six chronic diseases of interest in the study were identified and used as a summary of multi-drug counts. The BNF chapter for cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6, and for osteoarthritis under chapters 4 and 10. This means that overall; there were five main BNF chapters, which could constitute a measure of drug counts of up to a total of 5. The multi-drug count definition in this approach would then specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

Vascular comorbidity and drug prescribing for non-vascular conditions

The key likelihood of receiving drug treatments for the specific conditions of COPD, OA and depression in the study population with vascular comorbidity was also investigated. In this approach the 'vascular' comorbidity was defined as the group any one of diabetes, cardiovascular disease and cerebrovascular disease. The non-vascular groups were then individually compared with and without vascular comorbidity. For example, the COPD group was compared with vascular comorbidity to the COPD without vascular comorbidity, in relation to the likelihood of receiving COPD-specific drug treatment.

Whilst the key drug treatments for COPD, OA and depression can be examined in different ways such as the use of specific drugs, or drug doses and duration of drug therapy, we wanted to first establish the simplest likelihood of a patient given any one of the key group of drugs for COPD, OA or depression. The group of drugs derived from guidelines for COPD[10] included bronchodilators, corticosteroids, inhaled steroids and oxygen(BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for osteoarthritis[26] included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for depression[11] included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and 4.3).

Analysis

The first analyses was to describe the 2-year period prevalence of the 5 main BNF chapters in the specified chronic disease population, with a focus on some of the common drugs that were prescribed within each chapter expressed as drug prevalence/10,000 population aged 40 years and over, and differences were assessed using Chi-square tests. The five main chapter drug categories prevalence are described by age, gender and deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD) which is a composite score that is linked to postal address codes.[27] The IMD score was categorised into the bottom 20% (most deprived), middle 60% and the top 20% score (most affluent).

For each of the six chronic conditions, associations between the comorbid groups and higher multi-drug counts were compared to the respective reference 'alone' group. The 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and compared to 2 counts or less. Associations using logistic regression were expressed as Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios comparing prevalence of each drug count category in the comorbid group compared to the 'alone' group. Then for the vascular group, associations between each of the comorbid group with COPD, OA or depression were compared to the vascular 'alone' alone and higher multi-drug counts were then estimated.

Finally, the data was analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD and at least one of the vascular conditions; OA with at least one of the vascular conditions; and depression with at least one of the vascular conditions. Each group was the compared to their respective

vascular group e.g. COPD and vascular group compared to COPD without a vascular condition, by the specific optimal drug treatment. Association estimates using logistic regression are presented both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were carried out using SPSS version 17.0 statistical software.

Results

Study population

In the study population of 12,875 aged 40 years and over, the number of patients prescribed with cardiovascular system drugs were 9,384 (2-year time-period prevalence 73%), respiratory system drugs were 2,861 (22%), non-opioid analgesia were 5,395 (42%), anti-depressants were 3,241 (25%), anti-diabetic drugs were 2,916 (23%) and musculoskeletal system anti-inflammatory drugs were 2143 (17%) (**Table 1**).

In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% most ~~deprivation~~ deprived status were significantly more likely to be prescribed all main drug categories, except for the cardiovascular system (Chi-square test for trend $p<0.001$). For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were significantly higher for men compared to women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD ($p=0.462$). Prevalence figures were lower for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (Chi square test $p<0.001$ (**Table 2**)).

Individual chronic condition comorbidity and higher multi-drug counts

For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence numbers were greater for the individual groups without the other five comorbid conditions compared to the numbers for the individual conditions with comorbidity of other five conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone' ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for diabetes comorbid group.

Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-~~group~~ drug count compared to their respective 'alone' group ordered by

strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

Vascular condition comorbidity and higher multi-drug counts

The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group comorbid with OA OR 3.0 (2.6 to 3.5).

Comorbid vascular conditions and optimal non-vascular condition prescribing

The three specific non-vascular groups of COPD, OA and depression were compared with comorbid vascular conditions to without such vascular comorbidity in terms of their respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation, the association between the COPD and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared to their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).

Discussion

Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years and over with one of six specified and common chronic conditions showed the scale of multi-drug prescribing, which was higher in the presence of comorbidity compared to the respective index groups. Whilst previous evidence has shown the high levels of multiple

drug prescribing[15], our study findings link the disease status, comorbidity status to the measure of multi-drug prescribing for different systems.

Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or ~~the~~ non-vascular (COPD, OA or depression), the higher levels of multi-drug prescribing varied. All six conditions with comorbidity compared to their index condition had much higher multi-drug count, even adjusting for age, gender and deprivation. The measure of multi-drug count was notably distinct by the use of five different main drug chapter categories which were for different body systems, which means that this 'outcome' was not about multiple drugs use for the same condition. For example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different and distinct body systems, and not to the different drugs under the same chapter. The chronic condition of depression comorbidity had the strongest strength of association with higher multi-drug counts, followed by cardiovascular disease comorbidity, and the estimates of association for cerebrovascular disease, osteoarthritis and diabetes were similar. These findings suggest that the index condition and comorbidity may influence the range of multi-drug prescribing, and generates the interesting hypothesis on the potential variation in clinical outcomes of the index conditions may be because of underlying comorbid drug prescribing.

The study also grouped the vascular-related conditions to investigate the influence of non-vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of COPD, OA or depression). Again, the adjusted associations were significant, with vascular comorbidity being associated with higher-multi-drug counts compared to the respective 'vascular index' group. Here the clinical implication is that vascular comorbidity in populations aged 40 years and over might not only be associated with multiple vascular drugs as routinely suggested by clinical guidelines[28], but by a range of conditions such as comorbidity of COPD, OA or depression. It is possible that these conditions and the drug treatments for them may also in the end influence the health and healthcare outcomes of the index vascular conditions.[29]

In terms of the influence of comorbidity on key drug prescribing, our study findings show that vascular comorbidity in COPD and depression is associated with lower likelihood of drug prescribing for the respective conditions of COPD and depression. Similar findings, particularly for sub-optimal depression drug treatment, when depression is comorbid with chronic disease ~~has~~ have been shown previously.[30,31] However, such findings for osteoarthritis were not found, and here it is possible that the ~~'outcome'~~study definition of analgesia was too broad, as analgesia use covers a range of other painful conditions, in addition to osteoarthritis. Although the key drug definition was simple and broad, our study

findings seem to suggest that comorbidity does influence drug prescribing for specific conditions. Whether this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-disease interactions and the overall well-being of the patient is the important question raised by the findings.

The approach taken to looking at specific groups and six common conditions was based on a combination of clinical rationale and feasibility. Whilst, one could have investigated any number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the "vascular" level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be over-lapping of drug treatments. However, the "non-vascular" group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group-level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups. The study focus was also on comorbidity and further research is also required on how multimorbidity, defined as two or more conditions, influences the overall prescribing of multiple drugs and when the unit of analysis for outcome is not the disease but the arguably more important patient-centred outcomes.

The large scale study of specified chronic diseases was conducted using an anonymised database for a 2-year time-period. In terms of the cross-sectional associations, the findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer clinical implications as outlined earlier. However, the implications of the associations between comorbidity and the key drug definitions may be limited in this cross-sectional design and these may be treated cautiously as emergent findings. The chronic disease definitions were also based on routinely collected registers from general practices, which were and are part of a research network dedicated to the collection of clinical data in actual consultation. Whilst these chronic disease registers may be subject to variations in recording[32], the study analyses provide the estimates of association in actual clinical practice across 11 different sites.

The drug definitions were based on routinely coded repeat prescriptions and over a 2-year time-period represent an appropriate measure at the simpler but distinct broad system category. Patients however will also have been prescribed other drug categories outside of the five main categories that we had selected and for other less common conditions from the ones selected in the study, which means these drug levels are a specific estimate. The construction of our study defined index or 'alone' groups (without the other

5 conditions) provided the relative multi-drug level estimates to when the index condition was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone' group provide an estimate of main drug system prescribing without the associated condition (i.e. for other indications) compared to levels when there is a clear comorbidity record. However, this is time-defined by a 2-year time window, so some mis-classification may be possible and further research could explore how broad system drug definitions capture the underlying and specific common diagnostic categories. Further research is also required for the arguably more complex assimilation of the range of defined drug categories, other multi-morbidity and to investigate specific effect of individual drugs categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not available over the counter and are usually clinician prescribed. So it is possible that common over the counter drugs, particularly in relation to osteoarthritis, may be an under-estimate; however, the selection of repeated prescribing would mitigate against such under-estimation. Finally, although a large scale study, these general practices are drawn from one region of England, and whilst this might limit generalisability, the internal validity of the findings still remains.

In conclusion, our study findings show the links between common chronic conditions, comorbidity and associated multi-drug prescribing. The key and distinct finding is that the study shows that multi-drug prescribing defined by a range of selected but different systems is high in chronic conditions and higher in comorbidity. The common group of vascular conditions are not the only ones associated with their 'own' guideline driven multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and depression adds to the multi-drugs burden in patients. The importance of these findings, in addition to quantifying the scale, is whether such multi-drug therapy influences the quality of care for each of the individual conditions. Our findings suggest the potential for sub-optimal drug treatment as a consequence is in line with other evidence[33], but further research is required to investigate the impact of disease status, comorbidity, multi-drug therapy on prospective and long-term outcomes of clinical care.

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Data sharing: Data is not available for sharing under existing governance arrangements and no additional data is available.

Table 1: Prescribed drug prevalence by BNF main chapter and specific sections

BNF Chapter	BNF subsections	BNF Classification	Drug examples	Number	Drug prevalence/ 10,000†
2 Cardiovascular system				9384	7289
	2.9	Antiplatelet drugs	Aspirin, Clopidogrel Dipyridamole	*5044*	*3918*
	2.8	Anticoagulants	Warfarin	*669*	*520*
	2.2	Diuretics	Thiazide diuretics	*4912*	*3815*
	2.4	Beta blockers	Bisoprolol	*4034*	*3133*
	2.5	*ACE Inhibitors or *ARB	Ramipril, candesartan	*4250*	*3301*
	2.6	Nitrates, Calcium antagonists	GTN, Amlodipine	*4984*	*3817*
	2.12	Lipid regulating drugs	Simvastatin	*4894*	*3801*
3 Respiratory system				*2861*	2222
	3.1	Bronchodilators	Salbutamol	*2775*	*2155*
	3.2	Corticosteroids	Beclomethasone	*2140*	*1662*
	3.6	Oxygen	n/a	*94*	73
4 Central nervous system drugs				*7478*	5808
	4.7.1	Non-Opioid analgesics	Paracetamol	*5395*	*4190*
	4.7.2	Opioid analgesics	Codeine,Tramadol	*855*	*664*
	4.1	Hypnotics and anxiolytics	Diazepam	*1180*	917
	4.3	Selective Serotonin Reuptake Inhibitors Tricyclic Antidepressants	Fluoxetine, Citalopram, Amitriptyline	*3241*	2517
6 Endocrine system				*2916*	2265
	6.1.1	Insulin	Insulin, Humalog	*632*	*491*
	6.1.2	Oral anti-diabetic drugs	Metformin, Gliclazide	*2334*	*1805*

10 Musculoskeletal and joint disease				*2143*	1664
	10.1.1	Non-steroidal anti-inflammatory drugs	Ibuprofen, cyclooxygenase inhibitors	*2143*	*1664*

†*Population refers to those with one of six chronic conditions (n* = 12875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF) classification

Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	Musculo-skeletal System
Age (years)						
40-54	2738	1257 (46)	441 (16)	1447 (53)	555 (20)	378 (14)
55-69	4963	3712 (75)	1131 (23)	2694 (54)	1250 (25)	1003 (20)
70-84	4459	3807 (85)	1154 (26)	2824 (63)	1010 (23)	703 (16)
85 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
Gender						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
Deprivation**						
Deprived status	2609	1952 (75)	780 (30)	1705 (65)	695 (27)	474 (18)
Middle status	7228	5308 (73)	1538 (21)	4184 (58)	1616 (22)	1223 (17)
Affluent status	2203	1584 (72)	354 (16)	1185 (54)	419 (19)	377 (17)

***Deprivation measured by Index of Multiple of Deprivation, figures in brackets refer to the percentage of each study factor sub-group*

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Diabetes 'alone'	239	1178	4332	3120	1021	110	1.0
Diabetes comorbidity	58	492	2208	4523	2353	366	3.50 (3.0-4.2)
Prevalence ratio	*0.2*	*0.4*	*0.5*	*1.5*	*2.3*	*3.3*	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
Prevalence ratio	*0.2*	*0.3*	*0.9*	*2.6*	*8.3*	*7.6*	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
Prevalence ratio	*0.1*	*0.4*	*1.1*	*2.5*	*9.7*	*n/a*	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
Prevalence ratio	*0.20*	*0.4*	*0.8*	*1.5*	*5.00*	*n/a*	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
Prevalence ratio	*0.1*	*0.5*	*1.0*	*1.8*	*5.2*	*54*	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
Prevalence ratio	*0.17*	*0.34*	*1.15*	*4.58*	*13.7*	*n/a*	

**Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, **Comorbid drug ratio = 2-year drug count prevalence in the comorbid group/2-year drug count prevalence in the disease alone group; adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease*

Table 4: Associations between vascular comorbidity groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (95% CI)
	0	1	2	3	4	5	
Vascular group only*	199	2373	4018	2547	773	89	1.0
Vascular group and COPD	85	677	2854	4207	2008	169	4.63 (3.8-5.7)
Prevalence ratio	*0.43*	*0.29*	*0.71*	*1.65*	*2.60*	*1.90*	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
Prevalence ratio	*0.15*	*0.37*	*0.87*	*1.45*	*2.01*	*3.92*	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
Prevalence ratio	*0.35*	*0.35*	*0.93*	*1.54*	*1.76*	*1.03*	

**Vascular group only is the reference group without COPD, OA or depression; prevalence ratio is comparing vascular comorbid group with vascular group alone for each drug count category, adjusted for age, gender and deprivation and estimates are with the 'outcome' of higher drug count (3 to 4 combined) compared to lower drug counts (2 or less)*

Table 5: Key drug treatment of non-vascular conditions in vascular comorbidity

Numbers (%)	Key drug treatments		Unadjusted	Adjusted
	No	Yes	Odds Ratio (95% CI)	Odds Ratio (95% CI)
COPD without vascular comorbidity	123 (22)	937 (88)	1.0	1.0
COPD and vascular comorbidity	87 (19)	382 (81)	0.58 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

***Drug treatment for COPD, OA or depression respectively, adjusted for age, gender and deprivation as measured by Index of Multiple deprivation*

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.