Systematic examination of drug-disease and drug-drug interactions from following recommendations in 12 UK national clinical guidelines

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Systematic examination of drug-disease and drug-drug interactions from following recommendations in 12 UK national clinical guidelines

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Topic: Multimorbidity

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Abstract

Background and aim: There is increasing recognition that clinical guidelines may be problematic when applied to people with multimorbidity. Existing single condition clinical guidelines are not designed to consider the cumulative impact of multiple treatment recommendations on people with multimorbidity, which may result in risky combinations of drugs for individual patients. This study aimed to identify the number of drug-disease and drug-drug interactions for exemplar index conditions with National Institute of Health and Care Excellence (NICE) clinical guidelines.

Design and methods: Systematic identification, quantification and classification of potentially serious drug-disease and drug-drug interactions for drugs recommended by NICE clinical guidelines for each of the conditions type 2 diabetes, heart failure and depression, in relation to 11 other common conditions and drugs recommended by NICE guidelines for those conditions.

Results: There were 32 potentially serious drug-disease interactions between drugs recommended in the type 2 diabetes guideline and the other 11 conditions, compared to 6 for drugs recommended in the depression guideline, and 10 for drugs recommended in the heart failure guideline. Of these drug-disease interactions, 27 (84%), 6 (100%) and 10 (100%) for the respective index conditions were between the recommended drug and chronic kidney disease (CKD). There were a higher number of potentially serious drug-drug interactions identified between drugs recommended by each of the three index guidelines and drugs recommended by the guidelines for the 11 other conditions: 133 drug-drug interactions for drugs recommended in the type 2 diabetes guideline, 89 for depression and 111 for heart failure. Few of these drug-disease or drug-drug interactions were highlighted in the guidelines for the three index conditions.

Conclusions: Recommending drug treatment is central to most clinical guidelines, but guidelines currently rarely consider the likelihood or risks of drug-disease or drug-drug interactions. In this study, drug-disease interactions were found to be relatively uncommon with the exception of interactions when an individual has comorbid chronic kidney disease. Guideline developers could consider a more systematic approach regarding the potential for drug-disease interactions, based on epidemiological knowledge of the comorbidities of people with the disease the guideline is focused on, and should particularly consider whether CKD is common in the target population. In contrast, potentially serious drug-drug interactions between recommended drugs for different conditions were common. The extensive number of potentially serious drug-drug interactions requires innovative interactive approaches to the production and dissemination of guidelines to allow clinicians and patients with multimorbidity to make informed decisions about drug selection.

What is already known

- There is increasing recognition that clinical guidelines should better account for patients with multimorbidity.
- Many guidelines recommend drug treatments, but current guidelines rarely consider drug-disease or drug-drug interactions in these recommendations.

What this study adds

- For the 12 guidelines examined, drug-disease interactions were relatively uncommon, with the exception of interactions when an individual has comorbid chronic kidney disease.
- Potentially serious drug-drug interactions were common, although the harm caused will depend on both how commonly different conditions are comorbid, and the frequency and severity of the harm caused by the interaction.
- Guideline developers need to more explicitly account for drug-disease and drug-drug interactions in people with multimorbidity and should use epidemiological evidence to identify when interactions are likely to be common and serious enough to require specific mention in a guideline.
- Guideline developers are currently limited by the use of paper-based guidelines. Adaptive electronic-based guidelines that allow interactive searching for specific conditions are a potential way forward to account for multimorbidity in guideline recommendations.

Introduction

Despite widespread multimorbidity, clinical guidelines are largely written as though patients have a single condition and the cumulative impact of treatment recommendations from multiple clinical guidelines is not generally considered [1, 2]. In people with several conditions, simply applying recommendations from multiple single disease clinical guidelines can recommend complex, multiple drug regimens (polypharmacy) with the potential for implicitly recommending harmful combinations of drugs [3-5]. Clinical guidelines are of course not intended to be completely comprehensive guides to practice, in that clinicians are expected to use their judgment in deciding which therapies are appropriate in individual patients. There is, however, increasing recognition that clinical guidelines should better account for patients with multimorbidity [2, 6].

Adverse drug events (ADE) cause an estimated 6.5% of unplanned hospital admissions in the UK, accounting for 4% of hospital bed capacity. Where an admission ends in death, these are predominately the result of bleeding or renal injury [7]. While some ADEs are unpredictable (such as anaphylaxis from an unrecognised allergy), many others can be predicted and prevented, including drug-disease and drug-drug interactions [8]. ADEs as a cause for seeking ambulatory care in the USA nearly doubled between 1995 and 2005, with increasing age and increasing polypharmacy being the predominant patient characteristics associated with experiencing an ADE [4]. With an ageing population, and associated increasing multimorbidity, there is an increase in the potentially required number of drugs [9], and so the potential for increased risk of drug interactions [8, 10]. The American Geriatrics Society has identified the consideration of drug-disease and drug-drug interactions to be a key element of optimal care for older adults with multimorbidity [11].

This study aimed to quantify how often the drugs recommended by three exemplar National Institute of Health and Care Excellence (NICE) clinical guidelines have drug-disease interactions in the presence of other commonly comorbid conditions, or have potentially serious drug-drug interactions with drugs recommended by guidelines for these conditions.

Methods

Ethical approval was not required for this study which is entirely literature based. We selected three exemplar clinical guidelines produced by NICE, chosen because they were for common and important chronic physical and mental health conditions, (heart failure [12], type 2 diabetes [13], and depression [14]). Nine other NICE guidelines were then selected as potentially comorbid conditions based on: (i) being a common and chronic condition; (ii) being recently published; (iii)

including recommendations for the initiation of a drug treatment for a chronic condition, and (iv) being frequently comorbid with the three index conditions (figure 1). The nine selected other conditions were atrial fibrillation [15], osteoarthritis [16], chronic obstructive pulmonary disease (COPD) [17], hypertension [18], secondary prevention following myocardial infarction (post-MI) [19], dementia [20], rheumatoid arthritis [21], chronic kidney disease (CKD) [22], neuropathic pain [23]. For each of these guidelines, a panel of three clinicians (a general practitioner and two pharmacists) reviewed all recommendations made regarding the initiation of chronic drug treatments and identified 'first line' (recommended drug treatment for all or nearly all people with the condition; for example, angiotensin-converting enzyme (ACE) inhibitors for heart failure) and 'second line' drugs (recommended for some patients with the condition under some circumstances; for example spironolactone for people with heart failure and high levels of symptoms despite first-line treatment).

The expert panel then identified and classified drug-disease and drug-drug interactions and examined published guidelines to see if identified interactions were explicitly discussed. The British National Formulary (BNF) is the primary source used to obtain information on drug-drug and drug-disease interactions by UK clinicians [24]. For each of the three exemplar index guidelines the BNF was systematically searched to identify drug-disease warnings for guideline-recommended drugs, taking account of the predefined 11 conditions (the other two index conditions and the nine others). Drug-disease warnings were defined as being significant if a disease was stated to be a contraindication in relation to all or most people with the condition, or if the BNF stated that drugs should only be used with caution accompanied by a clear statement to avoid in all or most people with the condition. For chronic kidney disease (CKD) but not for other conditions, BNF warnings frequently recommended dose adjustment, and this was additionally counted for CKD.

The BNF categorises drug-drug interactions by severity and defines potentially serious interactions as ones where "concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)"[24]. Of note is that the 'potentially serious' designation is not an indication of the likelihood of an interaction, but of the seriousness of the potential harm if it occurs. The expert panel used the BNF to identify potentially serious interactions between drugs recommended by each of the three index guidelines and drugs recommended by any of the 12 guidelines (since two drugs recommended in the same guideline can interact). Each identified drug-drug interaction was then classified by the expert panel in terms of the type of potential adverse effect caused. Disagreement between panel members was resolved by discussion to reach a consensus view. The potential harm of included interventions were then classified into

one of the following categories: bleeding risk; central nervous system toxicity; cardiovascular adverse effect (including change in blood pressure, or effect on heart rate or rhythm); effect on renal function or serum potassium, or other. The 'other' classification included risk associated with changes in level of narrow therapeutic index drugs such as lithium carbonate, digoxin, and theophylline [25]. These classification categories were chosen to reflect the types of ADEs associated with emergency hospital admission [7].

Results

A total of four drugs, or classes of drug, were recommended as first line treatments and 19 second line treatments in the three exemplar clinical guidelines for type 2 diabetes. This compared with one drug class for first line and 12 drugs (or drug classes) for second line treatments for depression and two drug classes for first line and nine drugs (or drug classes) second line recommended for heart failure (see Appendix 1).

Table 1 summarises the number of times a drug recommended for each of the three index conditions would be contraindicated or should be avoided in the presence of any of the other 11 conditions. Drug-disease interactions were not common, with the exception of those related to CKD which affected type 2 diabetes in particular. CKD was involved in 27 of the identified 32 drug-disease interactions for drugs recommended in the type 2 diabetes clinical guideline and all of the six and ten drug-disease interactions for the depression and heart failure guideline, respectively. The guidelines for type 2 diabetes and heart failure each specifically discussed just one of these identified drug-disease interactions. For type 2 diabetes this recommendation was regarding the need to avoid thiazolidinedione treatment in people with comorbid heart failure. In heart failure, it was identified that amlodipine should be considered for the treatment of comorbid hypertension and/or angina in patients with heart failure, but verapamil, diltiazem or short acting dihydropyridine agents should be avoided. The depression guideline did not discuss any of the identified drug-disease interactions.

Potentially serious drug-drug interactions were common (see Figure 2). There were 133 potentially serious drug-drug interaction pairs identified for the type 2 diabetes guideline, of which 25 (19%) involved the four drugs recommended as first line treatments. Nine of the recommended drugs for diabetes did not have any drug-drug interactions. For the depression guideline, there were 89 potentially serious drug-drug interaction pairs identified, of which 19 (21%) involved the one drug class recommended as first line (SSRI antidepressants). For heart failure, there were 111 potentially

serious drug-drug interaction pairs identified, of which 21 (19%) involved the two drug classes recommended as first line (ACE inhibitors, and betablockers).

Figure 3 summarises the types of harm expected from potentially serious drug-drug interactions by index condition (see Appendix 2 for further detail). For type 2 diabetes, cardiovascular-related harm such as significant hypotension or bradycardia was the most frequent category, followed by 'other' (which includes increased lithium or digoxin levels causing risk of toxicity, and myopathy with statin therapy), and renal or serum potassium associated harms. For depression, bleeding risks were the most commonly identified harms, particularly involving SSRIs recommended first line, followed by 'other' harms (most commonly relating to lithium toxicity), and cardiovascular and central nervous system (CNS) toxicity. The majority of cardiovascular adverse effects in the depression guideline were related to increased risk of ventricular arrhythmias. The most common potentially serious drug interactions for the heart failure guideline were for bleeding events, but also drug interactions causing severe hypotension or related to increased digoxin or lithium levels causing risk of toxicity.

A very limited number of the identified drug-drug interactions were highlighted in the index guidelines. In the guideline for type 2 diabetes, only two interactions were mentioned: potassium sparing diuretics with ACE inhibitors; and potassium sparing diuretics with angiotensin receptor blockers. The depression guideline highlighted only the increased risk of bleeding with SSRIs plus NSAIDs or aspirin. None of the recommendations in the heart failure guideline contained an explicit discussion of the 111 potentially serious drug-drug interactions identified.

Discussion

Many guidelines suggest commencing a drug treatment, but currently guidelines rarely consider drug-disease or drug-drug interactions in their recommendations. In this study, potentially serious drug-drug interactions were found to be relatively common among guideline recommendations for each of three index conditions and 11 other common conditions. In contrast, drug-disease interactions were found to be relatively uncommon with the exception of interactions when an individual has comorbid chronic kidney disease. The types of harm potentially introduced by co-prescription of drugs varied by clinical guideline and was most commonly related to: cardiovascular and 'other' for diabetes recommended drugs; bleeding and 'other' for depression; and bleeding and cardiovascular for heart failure.

Previous studies of the implications of following single disease guidelines in people with multimorbidity have usually considered single, hypothetical patients with carefully selected multiple conditions which is likely to overstate the scale of the problem [5, 26]. Using United States

population survey data, Lorgunpai et al found a much higher rate of drug-disease interactions (which they termed 'therapeutic competition') with one-fifth of older American adults being prescribed drugs for one condition with the potential to worsen another [27]. However, their study included interactions which did not reach our threshold of being recommended to avoid in all or most patients (for example the use of beta-blockers for coronary heart disease in people with chronic obstructive pulmonary disease was common in their study, but although it carries some risk is not stated as a contraindication or recommendation to avoid in the BNF because the benefits outweigh the harms in most patients).

One key potential limitation is the use of a selection of clinical guidelines as exemplar case studies, and some other guidelines do discuss interactions in more detail. For example, NICE have produced a guideline for depression in people with a chronic physical health problem [28] which includes extensive discussion about drug interactions (although in a full guideline appendix which will not be commonly read by clinicians), or their guideline on management of bipolar disorder [29], which includes detailed recommendations about safe use of lithium. However, we would not expect the pattern of findings to be substantially different for other guidelines which include a reasonable number of recommendations for chronic drug treatment. Any recommendations for commencing drugs for acute conditions were excluded from this analysis, but it should be noted that interactions with drugs like antibiotics and NSAIDs used for short-term intercurrent illness are common and important [3]. The inclusion of additional guidelines would have further increased the number of potential interactions identified. Both of these exclusions imply that our findings are likely to be conservative.

This study systematically examined recent national guidelines produced by NICE for important and common clinical conditions, using data on interactions drawn from a single, authoritative UK source. Defining contraindications and potentially serious interactions was not straightforward, reflecting that the risk of such events is often poorly quantified and information sources vary in what is rated to be significant [30]. This study used the BNF because it is the reference source used by most UK-based clinicians. The BNF draws on data from manufacturer Summary of Product Characteristics (SPC), the medical literature and expert opinion, but other reference sources might not be consistent with this and a databases of listed potentially serious drug interactions may have yielded different results. For example, an SPC for amitriptyline from the online electronic medicines compendium of up to date, approved and regulated prescribing information for licensed medicines [31] includes cardiac arrhythmias and history of myocardial infarction as contraindications but these are not listed in the BNF.

We recommend that during the development of clinical guidelines the process could consider how to more explicitly identify and highlight the potential for interactions between drugs recommended, and other conditions and other drugs that patients with the guideline condition are likely to have [32, 33]. It is important to acknowledge that guideline developers have to walk a fine line between producing clear and relatively short recommendations, and avoiding glossing over the complexity of the real world [34].

For the conditions examined in this study, major drug-disease interactions were relatively rare with the exception of CKD where they were more common. An implication is therefore that guideline developers should always explicitly decide whether CKD is common enough in the real-world population with the disease under consideration to require comment or modification of recommendations. For the three index conditions examined here, CKD comorbidity prevalence was 4.1% in depression, 13.5% in type 2 diabetes and 23.0% in heart failure, and so the implication might be that guideline developers should consider CKD with heart failure, possibly consider it with type 2 diabetes and possibly not consider it with depression.

Potentially serious drug-drug interactions were much more common, but there are too many for all of them to be specifically mentioned by guidelines. From this perspective, we suggest that clinical guidelines produced and disseminated using a paper-based format will only ever be able to adequately account for a minority of potential drug-drug interactions. Guideline developers should acknowledge potentially serious drug-drug interactions and estimate their likely frequency and severity. Frequency will be determined both by whether the drug being recommended is first line (intended for all or nearly all people with the condition), by how commonly interacting drugs are used which will depend on rates of comorbidity, and by how common the ADE in question occurs. Of note is the requirement for detailed information about the real-world population that the guideline is making recommendations for, which is currently much less commonly used in guideline development than trial data from narrowly selected populations. With the growth of large electronic primary care datasets, it is now reasonably straightforward to define the population that recommendations are being made for, and describe its demography, comorbidity and current prescribing. As an example, there is a potentially serious interaction between statins recommended first-line for patients with type 2 diabetes and ciclosporin recommended second line for rheumatoid arthritis, due to risk of myopathy (and rhabdomyolysis). Given that only 1.4% of people with type 2 diabetes also have rheumatoid arthritis and ciclosporin is only recommended second-line for rheumatoid arthritis, this will only ever be a very rare drug-drug interaction and so is very unlikely to reach the threshold for explicit consideration by a guideline development group. In contrast, co-

prescription of SSRI antidepressants (recommended first-line for depression), and tramadol (recommended second-line for painful conditions), is likely to be common because tramadol is commonly used for pain in the UK and 27.1% of people with depression also have painful conditions [1, 35]. However, although potentially fatal, the risk of serotonin syndrome appears to be low although it is poorly quantified,[36] and the guideline development group will have to make a judgement as to whether they believe the interaction requires specific mention to inform clinicians and patients to be aware of the signs and symptoms of serotonin syndrome should they occur. The key issue is that interactions and risks should be systematically assessed and explicit decisions made about whether they require discussion, similar to the requirement for treatment benefits to be systematically and explicitly assessed. Details of expected harm from the identified potentially serious drug-drug interactions (such as those in appendix 2), could be considered to inform clinicians about alternative drug choices, or to inform their discussions with individual patients.

One of the challenges for guideline developers is that the actual harms of many drug-drug and drug-disease interactions are poorly quantified, partly reflecting that whereas clinical trials produce high-quality evidence about benefit, they are poorly suited to estimating harms, particularly in real-world populations who are typically older, frailer, more multimorbid and prescribed more drugs for other conditions compared to trial populations [37]. Research is needed to more systematically quantify these harms since understanding when harms outweigh benefits is critical for rational treatment decisions. Paper-based single disease guidelines are intrinsically limited by being hard to integrate for people with multiple conditions, and by being unable for reasons of length and usability to document all possible interactions. In principle, guidelines embedded in electronic medical records which integrate recommendations for all the conditions an individual has could address the problem identified in this paper, but the best design and effectiveness of such guidelines requires research [38].

Licence

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that the work reported is part of the Better Guidelines for Better Care study funded by the National Institute for Health Research Health Services and Delivery Programme (NIHR HS&DR 11/2003/27). The funder had no role in design or conduct of the study or the decision to publish. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HS&DR Programme, NIHR, the National Health Service or the Department of Health. There are no financial relationships with any organisations that might have an interest in the submitted work in the previous three years no other relationships or activities that could appear to have influenced the submitted work; other than, Dr. Alderson who reports that he is a full time employee of NICE working on the development of clinical guidelines, but the views in the paper are personal and do not represent the views of NICE; and Dr Nairn who reports that he is a full time employee of Scottish Intercollegiate Guideline Network (SIGN) working on the development of clinical guidelines, but the views in the paper are personal and do not represent the views of SIGN.

Contributorship

SD, AF, BG, MN, ST, SM, MW, PA, AT, KP were involved in the design of the study, SD, AF and BG on data collection and analysis, SD wrote the first draft and all authors revised or commented on the manuscript. SD is the guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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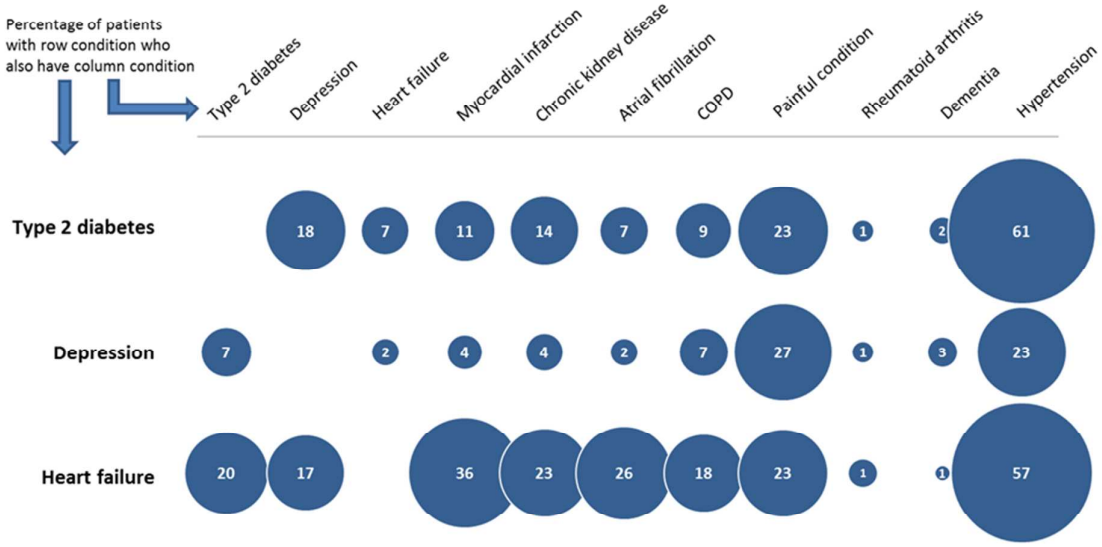
Figure 1: Percentage of people with the three index conditions who have each of the other conditions*



* Morbidity data was not available for osteoarthritis or neuropathic pain; the 'painful condition' data shown are defined by receipt of four or more prescriptions for non-over the counter analgesics in the previous 12 months.

Table 1: Number of drug-disease interactions between drugs/drug classes recommended for each index condition and the 11 other conditions.

Index conditions	CKD (dose change)	CKD (avoid)	Heart Failure	Depression	Type 2 Diabetes	Atrial Fibrillation	Osteoarthritis	COPD	Hypertension	Post MI	Dementia	Rheumatoid Arthritis	Neuropathic Pain	Total
Type 2 Diabetes[1]														
First line*	3	2	0	0	n/a	0	0	0	0	0	0	0	0	5
Second line**	11	11	5	0		0	0	0	0	0	0	0	0	27
Depression[2]														
First line	1	0	0	n/a	0	0	0	0	0	0	0	0	0	1
Second line	2	3	0		0	0	0	0	0	0	0	0	0	5
Heart Failure[3]														
First line	2	1	n/a	0	0	0	0	0	0	0	0	0	0	3
Second line	3	4		0	0	0	0	0	0	0	0	0	0	7

*First line drug = explicitly described as a first-line drug, or recommended for (almost) everyone with the condition.

**Second-line/other drugs = explicitly described as a second or third line drug, or recommended for only some subgroups or in some not very common circumstances

1.- CG87 Type 2 Diabetes: First line: metformin, sulphonylurea, angiotensin-converting enzyme inhibitors (ACEI), simvastatin/atorvastatin. Second line/other: angiotensin-II receptor antagonists (ARB) for hypertension, calcium channel blocker for hypertension, diuretic for hypertension, alpha blocker for hypertension, beta blocker for hypertension, K-sparing diuretic for hypertension, other statins (not simvastatin/atorvastatin), fibrate, erythromycin, phosphodiesterase type-5 inhibitors (PPDE5 inhibitors), metoclopramide, ezetemibe, omega-3 fish oil, domperidone, DPP-4 inhibitor/gliptin, thiazolidinedione, GLP-1 mimetic (exenatide), acarbose, insulin.

2. CG90 Depression: First line: Selective serotonin reuptake inhibitors (SSRIs). Second line: venlafaxine, mirtazepine, duloxetine, reboxetine, flupenthixol, tryptophan, mianserin, tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), moclobemide, lithium, antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone)

3. CG108 Heart Failure: First line: ACEI, beta blocker licensed for heart failure. Second line/other: licensed aldosterone antagonist, digoxin, ARB, hydralazine, nitrate, loop diuretic, warfarin, amlodipine if comorbid hypertension/angina, aspirin if comorbid coronary heart disease.

Table 2. Type of expected harm from potentially serious drug-drug interaction for each index condition.

Index condition	Cardiovascular†	Bleeding	Renal/ Potassium	Central nervous system	Other*	Total
Type 2 Diabetes						
First line recommended drug	3	3	2	0	12	20
Second line recommended drug	54	11	18	1	29	113
Depression						
First line recommended drug	1	9	0	7	2	19
Second line recommended drug	10	13	0	0	20	70
Heart Failure						
First line recommended drug	15	0	4	0	2	21
Second line recommended drug	17	34	17	0	22	90

† 'Cardiovascular' ADEs includes effects on heart rate or rhythm or effects on blood pressure.
* 'Other' ADEs includes myopathy with statin therapy, or clinically significant altered plasma concentration (for example of digoxin, lithium, ciclosporin or theophylline) which might require dosage alteration or closer monitoring.

Figure 2: Potentially serious drug-drug interactions between drugs recommended by clinical guidelines for the three index conditions and drugs recommended by each of the other 11 other guidelines.

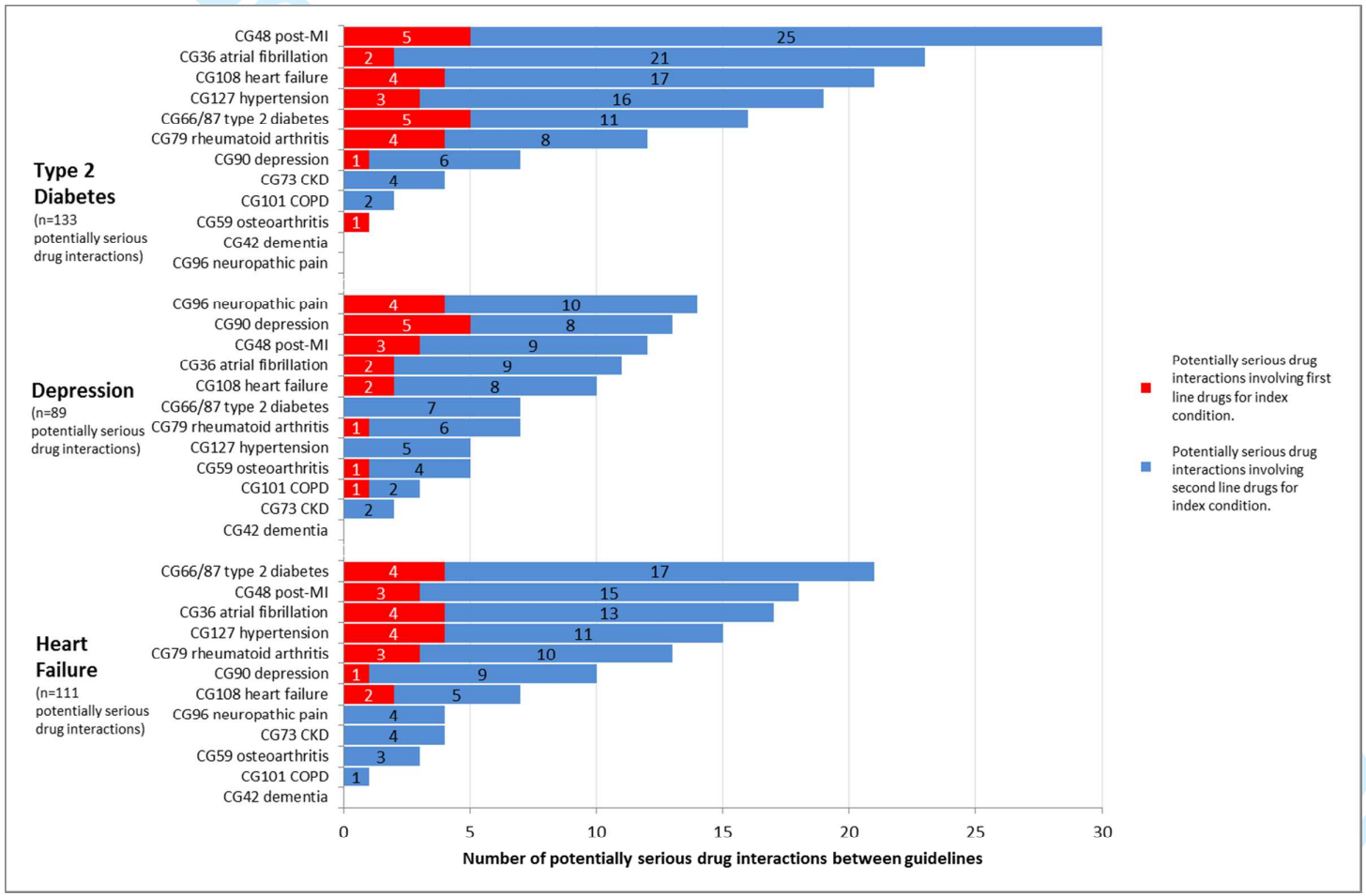
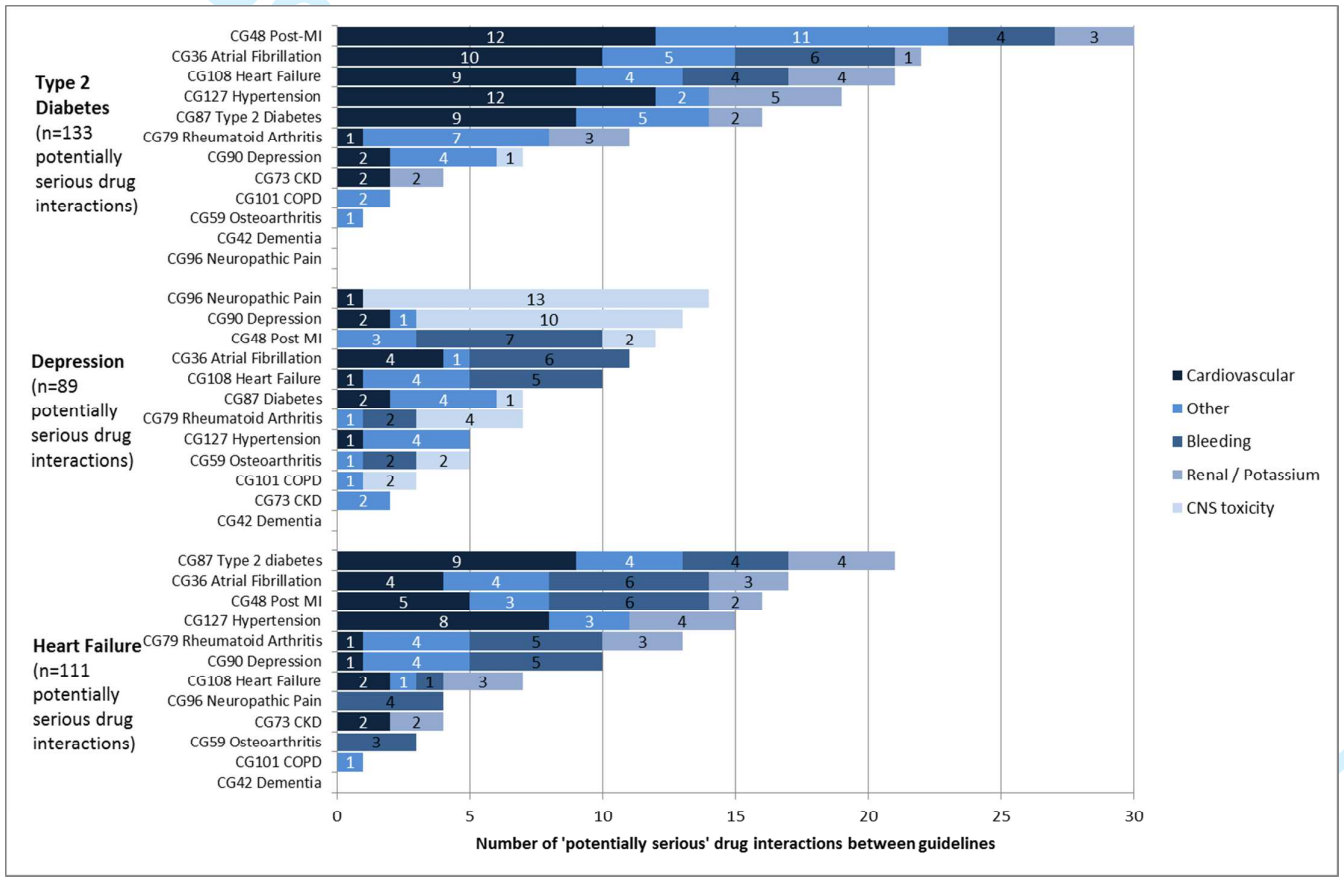


Figure 3. Types of potentially serious harm from drug-drug interactions between drugs recommended by clinical guidelines for the three index conditions and drugs recommended by each of the other 11 other guidelines.



Appendix 1

First and second line drugs recommended in 12 selected NICE Clinical Guidelines.

Definitions

First line drug = explicitly stated to be a first-line drug, or recommended for (almost) everyone with the condition.
Second-line/other drugs = explicitly stated to be a second or third line drug, or recommended for only some subgroups or in some not very common circumstances

Identified first and second line drugs

1.- CG87 Type 2 Diabetes
First line: Metformin, sulphonylurea, angiotensin-converting enzyme inhibitors (ACEI), simvastatin/atorvastatin.
Second line/other: Angiotensin-II receptor antagonists (ARB) for hypertension, calcium channel blocker for hypertension, diuretic for hypertension, alpha blocker for hypertension, beta-blocker for hypertension, K-sparing diuretic for hypertension, other statins (not simvastatin/atorvastatin), fibrate, erythromycin, phosphodiesterase type-5 inhibitors (PPDE5 inhibitors), metoclopramide, ezetemibe, omega-3 fish oil, domperidone, DPP-4 inhibitor/gliptin, thiazolidinedione, GLP-1 mimetic (exenatide), acarbose, insulin.

2. CG90 Depression
First line: Selective serotonin reuptake inhibitors (SSRI).
Second line: Venlafaxine, mirtazepine, duloxetine, reboxetine, flupenthixol, tryptophan, mianserin, tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), moclobemide, lithium, antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone)

3. CG108 Heart Failure
First line: ACEI, beta blocker licensed for heart failure
Second line/other: Licenced aldosterone antagonist, digoxin, ARB, hydralazine, nitrate, loop diuretic, warfarin, amlodipine if comorbid hypertension/angina, aspirin if comorbid Coronary Heart Disease

4. CG36 Atrial Fibrillation
First line: Warfarin, aspirin, standard beta blocker, rate limiting calcium channel blocker.
Second line/other: Phenindione, dabigatran etc , digoxin, sotalol, amiodarone, class 1c flecainide, class 1c propafenone

5. CG42 Dementia
First line: Donepezil, galantamine, rivastigmine.
Second line/other: memantine.

6. CG 48 Secondary Prevention Post–MI
First line: ACEI, aspirin. beta-blocker, statin.

Second line/other: ARB, clopidogrel, warfarin, diltiazem if beta-blocker contraindicated/not tolerated or hypertension/angina and not heart failure, verapamil if beta-blocker contraindicated/not tolerated or hypertension/angina and not heart failure, amlodipine for hypertension/angina and heart failure, proton pump inhibitor (PPI), aldosterone antagonist licensed post-MI, fibrates if intolerant of statin, omega 3 fatty acids, PPDE5 inhibitors, nicotine replacement therapy (NRT), bupropion.

7. CG59 Osteoarthritis
First line: Paracetamol, topical NSAID.
Second line/other: Oral non-selective NSAID, Cyclo-oxygenase-2 selective inhibitors, PPI if on NSAID, opioids (codeine/dihydrocodeine), topical capsaicin.

8. CG73 CKD
First line: ACEI
Second line/other: Statins, antiplatelets, antihypertensives, ARB, vitamin D supplements, bisphosphonate.

9. CG79 Rheumatoid Arthritis
First line: Methotrexate, sodium aurothiomalate, penicillamine, hydroxychloroquine, chloroquine, azathioprine, ciclosporin, leflunomide, sulfasalazine
Second line/other: Adalimumab, etanercept, infliximab, paracetamol, c odeine, dihydrocodeine, NSAIDs, Cyclo-oxygenase-2 selective inhibitors, PPI

10. CG96 Neuropathic Pain
First line: Amitriptyline, pregabalin.
Second line/other: Imipramine, nortriptyline, topical Lidocaine, tramadol, duloxetine for painful diabetic neuropathy.

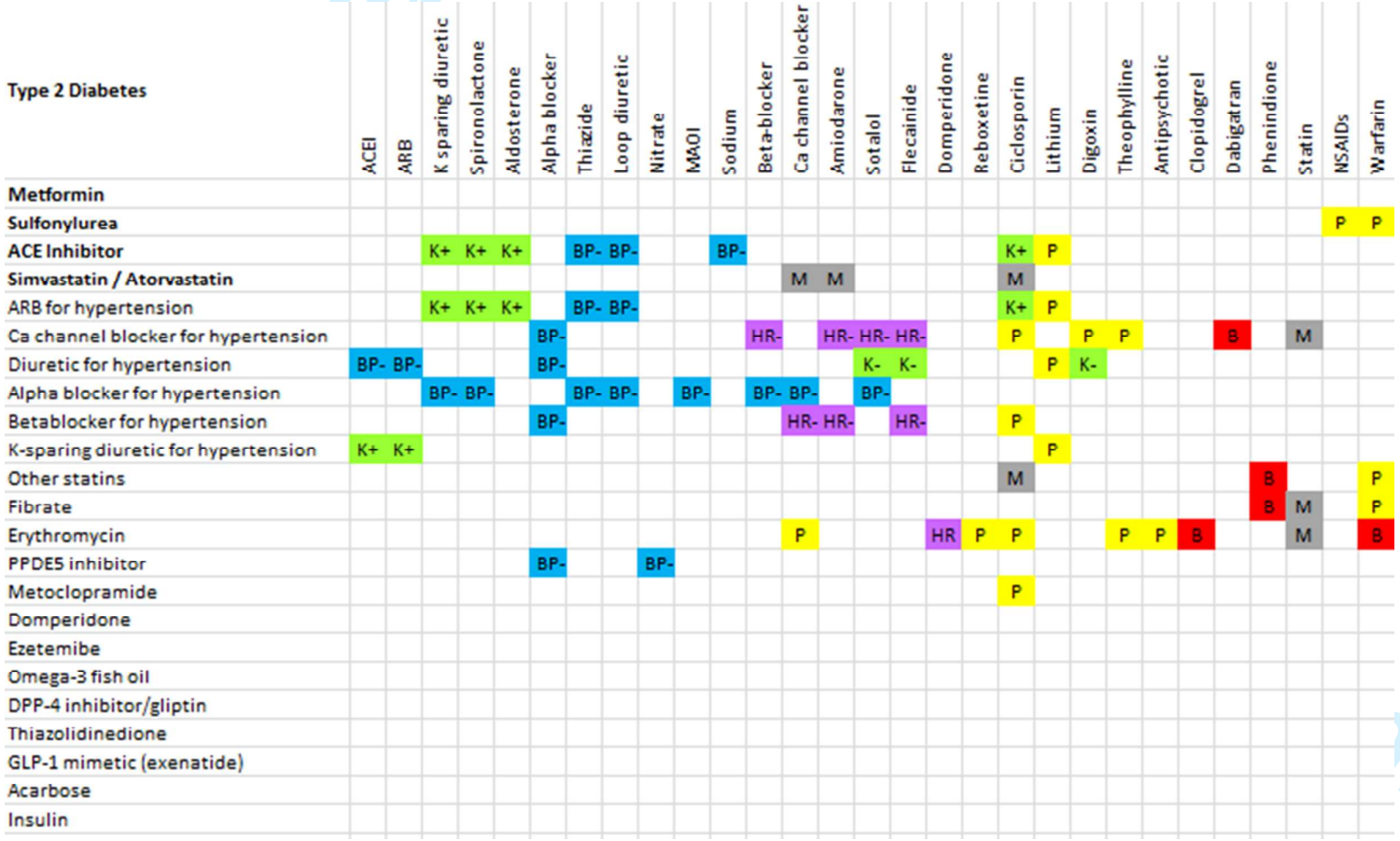
11. CG101 COPD
First line: Short-acting beta2 agonist (SABA), short-acting muscarinic antagonist (SAMA).
Second line/other: Long-acting muscarinic antagonist (LAMA), long- acting beta2 agonist (LABA), inhaled corticosteroid, theophylline, mucolytic, NRT, varenicline, bupropion.(Excluded: palliative, oxygen, long term steroids, osteoporosis)

12: CG127 Hypertension
First line: ACEI, ARB, calcium channel blocker, thiazide like diuretic.
Second line/other: Spironolactone, beta blocker, alpha blocker.

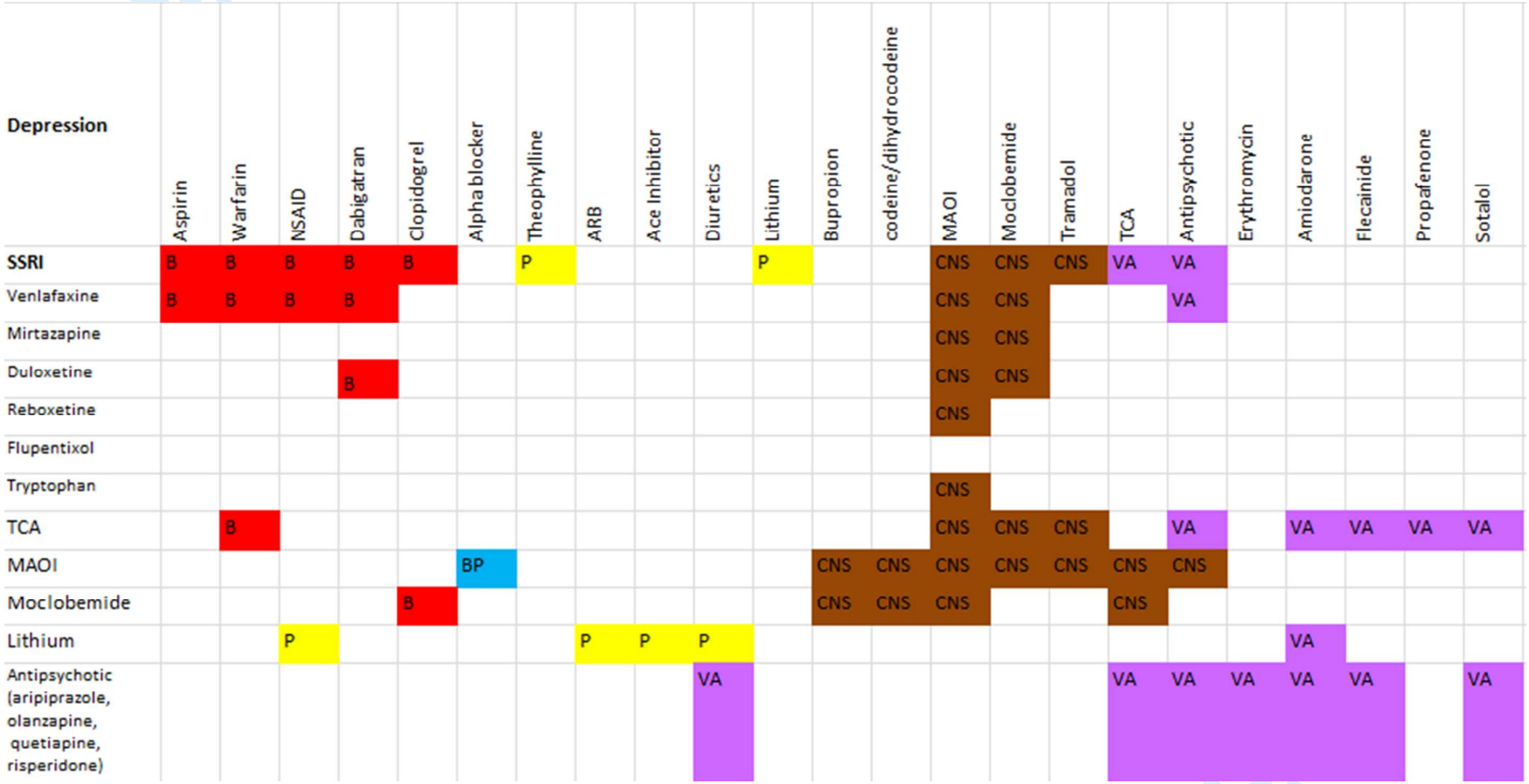
Appendix 2

Details of expected harm from the identified potentially serious drug-drug interactions for each of the three index conditions.

Index condition **Interacting drugs recommended by any of the 12 guidelines**



Index condition **Interacting drugs recommended by any of the 12 guidelines**



Index condition **Interacting drugs recommended by any of the 12 guidelines**

HEART FAILURE	Alpha blocker	Sodium Aurothiomalate	PPDES inhibitor	Diuretic for BP	ACE Inhibitor	Angiotensin-II receptor antagonist	Digoxin	K+sparing diuretic	Flecainide	Sotalol	Amisulpride / Pimozide	Amiodarone	Propafenone	Ciclosporin	Verapamil	Diltiazem / Nifedipine	Nicardipine	Hydroxychloroquine Chloroquine	Lithium	Theophylline	Methotrexate	Phenindione	NSAIDs / COX2	SSRI	Venlafaxine	Erythromycin	Simvastatin	Sulphonylurea	Aspirin Azathioprine Clopidogrel Dabigatran Esomeprazole Fibrates Fluvastatin Omeprazole Rosuvastatin TCA Tramadol
Licenced Betablocker	BP-								HR-			HR-	HR-	P	BP-	HR-													
ACE I		BP-		BP-				HK						HK					P										
Aldosterone antagonist					HK	HK	P	HK						HK					P										
Digoxin				LK								P	P	P	P	P	P	P											
Angiotensin-II receptor antagonist				BP-				HK						HK					P										
Hydralazine																													
Nitrate			BP-																										
Loop diuretic	BP-				BP-	BP-	LK		LK	LK	LK								P										
Warfarin												B	B										B	B	B	B		P	B
Aspirin																					P	B	B	B	B				
Amlodipine	BP-																			P						P	M		

Key:

BP- = hypotensive effect; B=bleeding; HR-= bradycardia; VA = ventricular arrhythmias; LK/HK = effect on serum potassium; P= clinically significant altered plasma concentration which might require dosage alteration or closer monitoring; M=myopathy; CNS = central nervous system toxicity.