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# An international consensus list of potentially clinically significant drug-drug interactions in older people

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**Brief summary** - We established an explicit list of potentially clinically significant DDIs relevant to people aged ≥ 65 years, using a Delphi process with a European expert panel. The list can be used in clinical practice, education and research.


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## ABSTRACT

**Objectives:** We aimed to establish an explicit list of potentially clinically significant DDIs in people aged ≥ 65 years.

**Design:** A preliminary list of potentially clinically significant DDIs was compiled, based on 154 DDIs identified from literature review. Subsequently, a two-round online Delphi survey was undertaken with a multidisciplinary expert panel. A consensus meeting and a final round were conducted to validate the final DDI list and the scope of information provided.

**Setting and Participants:** 29 experts, including geriatricians and clinical pharmacists from eight European countries

**Measures:** For each DDI, in the first two rounds, experts were asked to score the *severity of potential harm* on a five-point Likert scale. DDIs were directly included on the final list if the median score was 4 (major) or 5 (catastrophic). DDIs with a median score of 3 (moderate) were discussed at a consensus meeting and included if ≥75% of participants voted for inclusion in the final round.

**Results:** Consensus was achieved on 66 potentially clinically significant DDIs (28 had a median score of 4/5 and 48 of 3 in the Delphi survey). Most concerned cardiovascular, antithrombotic, and central nervous system drugs. The final list includes information on the mechanism of interaction, harm, and management. Treatment modification is recommended for three-quarters of DDIs.

**Conclusion and implications:** We validated a list of potentially clinically significant DDIs in older people, which can be used in clinical practice and education to support identification and management of DDIs or to assess prevalence in epidemiological and intervention studies.

## INTRODUCTION

Drug-drug interactions (DDIs) are common in older people and are associated with an increased risk of adverse drug events and hospitalisation.[1,2] Older adults are particularly susceptible to DDIs because of multimorbidity, polypharmacy, age-related changes in pharmacokinetics (i.e. the absorption, distribution, metabolism and elimination of drugs) and pharmacodynamics (i.e. the relation between the concentration of a drug and the response obtained) and treatment by multiple care providers.[2-4] Reported prevalence rates of DDIs in older people vary widely across studies (1.5% to 55%), reflecting variation in study population, setting, definitions and information sources used.[1,3,5,6] The severity of DDIs varies considerably and only a proportion of all DDIs leads to adverse clinical consequences.[3,5] These clinically significant DDIs are particularly important to detect, as they are a preventable cause of morbidity and mortality.[3,6,7]

It has been proposed that consensus is needed for identifying clinically significant DDIs in order to generate comparable results across studies.[5] Moreover, clinically significant DDIs have been recently selected as one of the core outcomes for clinical trials of medicines optimisation in older people.[8,9] While a number of explicit tools to screen for potentially inappropriate prescribing (including DDIs) in older people are available,[10] no list of potentially clinically significant DDIs validated specifically for use in older people exists. We aimed to establish an explicit list of potentially clinically significant DDIs relevant to people aged ≥65 years.

## METHODS

A list of potentially clinically significant DDIs in older people was developed in four steps: a literature review to compile a preliminary list of DDIs for inclusion in the Delphi survey; a two-round Delphi survey, followed by a consensus meeting and final round; compiling the final list (Appendix 1).

1. Literature review

A systematic overview of inappropriate prescribing assessment tools (i.e. their first table that identified tools with DDI items[10])- and the authors' knowledge of the published literature base served as a starting point to identify explicit DDI lists in older people. Furthermore, we searched PubMed using the terms 'Drug Interactions' and 'Potentially Inappropriate Medication List'. Articles published between January 1990 and March 2018 were eligible if they contained a list of DDIs in older patients. Other types of studies (e.g. case reports, studies evaluating a specific DDI) were excluded. We performed a manual search from the reference list of included articles. Only the latest available version of the DDI list was included.

The research team reviewed the DDIs retrieved in the lists and made the following modifications: DDIs reported by only one list and not classified as a major interaction by recognised DDI sources *(Micromedex and/or UpToDate)* were excluded; some DDIs were merged (i.e. when there was overlap); DDIs with direct oral anticoagulants (DOACs) were not reported in any of the DDI lists retrieved from the literature but were added based on data from review papers [11,12] and from experimental and pharmacoepidemiologic studies (full list of references available upon request) .

2. Two-round Delphi survey

Experts from nine centres in eight countries (Belgium, Iceland, Ireland, Italy, The Netherlands, Spain, Switzerland and United Kingdom) were invited to participate in the survey by e-mail. Experts included pharmacists and physicians with (a) experience in geriatric medicine or research experience in quality of prescribing and (b) involvement in either the SENATOR or OPERAM trials evaluating medicines

optimisation in older people.[13,14] We aimed for 4 participants, with a minimum of one physician and one pharmacist, per country. Experts who did not take part in one Round were excluded for the next Round.

A modified two-round Delphi survey was conducted by e-mail between June and July 2018. In Round 1, panellists were asked to score, for each DDI from the preliminary list, the *severity of potential harm* (defined as the impact of the DDI) on a five-point Likert scale (1=insignificant, no risk of patient injury or harm and no intervention required; 2=minor, minor injury or illness requiring minor intervention; 3=moderate, moderate injury requiring intervention; 4=major, major injury requiring intervention; 5=catastrophic, leading to death, multiple permanent injuries, or irreversible health effects[15]). Each DDI included a brief explanation concerning the type of interaction (pharmacodynamics [i.e. drugs with additive or opposing effects] or pharmacokinetic [i.e. one drug affects the absorption, distribution, metabolism or elimination of another drug]), mechanism, potential harm and the number of existing lists mentioning the particular DDI. A box was provided for each DDI to allow for comments. Panellists could also propose additional DDIs. Panellists were instructed to score the severity of potential harm, assuming that the drug was prescribed at a normal dose, the prescriber had not taken into account a possible DDI and did not put in place preventive interventions. Panellists were also instructed to avoid consideration of the frequency of use of the drug. When several adverse consequences for a certain DDI were listed as 'potential harm', panellists were asked to score the severity for the most serious consequence.

For each DDI, consensus measurement was based on the median score and the interquartile range, as suggested and used in previous research.[16,17] The cut-off values for consensus measurement were pre-defined: DDIs with a median score of ≥4 and P25 ≥3 were directly included in the final list of DDIs; DDIs with a median score of <3 were directly excluded; DDIs with a median score of 3 were neither included nor excluded but were re-evaluated in Round 2.

In Round 2, panellists were asked to re-evaluate the DDIs with a median score of 3 from Round 1 on the five-point Likert scale. Panellists were provided with a reminder of their own responses from Round 1, the

median group score and the interquartile range. Furthermore, panellists were asked to evaluate the DDIs that were newly proposed in Round 1 and space for comments and proposal of additional DDIs was provided. After Round 2, the DDIs that did not meet the cut-off values for direct inclusion/exclusion were discussed in a consensus meeting.

After each round, participants' comments were scrutinised and considered carefully prior to preparing the next step of the study.

3. Consensus meeting and final round

A consensus meeting was performed by teleconference. The results of the Delphi survey were presented. The aim of the consensus meeting was to discuss how to address the set of DDIs with a median score of 3 from Round 2, to agree on the possibility to merge or split-up certain DDIs (based on comments made by panellists or by the research team) and to decide on the information to be provided in the final DDI list. To maximise feasibility, we aimed to have one participant per country, and both professions (pharmacists and physicians) represented. A final round was then conducted with all participants from Round 2. A summary of the results from Round 2 and of the consensus meeting were provided. Each participant was asked to specify whether or not, for each DDI that had a median score of 3 at round 2, this DDI should be included in the final list. A DDI was included if ≥75% of participants rated it YES in this final round.

4. Compiling the final list of DDIs

To compile a DDI list that can be applied in practice, the mechanism, the potential harm and management of the DDI were added to the final list. *Micromedex, Stockley's Drug Interactions, UpToDate* and *Drugs.com* were used as drug interaction compendia. The final table was double-checked by members of the Delphi panel for accuracy.

## RESULTS

An overview of the DDIs evaluated and included at each step of the process is available in Appendix 1.

1. Literature review to compile a preliminary list of DDIs

Eleven explicit lists including 154 DDIs were retrieved from the literature (Table 1).

Following review by the research team, 49 DDIs were removed (not classified as major by DDI sources), 50 DDIs were modified (i.e. merged) and two DDIs with DOACs were added, resulting in a total of 74 DDIs for inclusion in the Delphi survey.

2. Two-round delphi survey

Of the 35 healthcare professionals who were invited, 29 (82.9%) and 28 (80.0%) completed Round 1 and 2, respectively. Delphi panellists included 12 geriatricians, 15 pharmacists and two internal medicine specialists from eight European countries. Fourteen, seven and eight panellists had >15 years, 6-15 years and 0-5 years of practice experience, respectively.

Out of the 74 DDIs presented in Round 1, there was consensus to include 23 DDIs in the final DDI list and to exclude six DDIs. Forty-five DDIs had a median score of 3 and were re-evaluated in Round 2. Eight additional DDIs were suggested by panellists. Out of the 53 DDIs presented in Round 2, there was consensus to include five DDIs and to exclude one DDI. Forty-seven DDIs with a median score of 3 were discussed in the consensus meeting. In Appendix 2, the median score of each DDI after Round 1 and 2 is provided.

3. Consensus meeting and final round

Eight experts (5 geriatricians, 2 pharmacists and 1 internal medicine physician from eight countries) took part in the consensus meeting. They recommended that the DDIs with a median score of 3 should be

included on the final list. Hence all DDIs included on the final list require an intervention (median score ≥ 3). Twenty-four Delphi participants completed the final round. Consensus was not achieved (i.e. <75% of participants rated YES) for 3 DDIs (Appendix 3).

The list of excluded DDIs is presented in Appendix 4.

4. Compiling the final list of DDIs

After merging or splitting-up certain DDI pairs (in case of overlap or differences in the type or management of DDI, based on suggestions by panellists and research team members), the final list comprises 66 potentially clinically significant DDIs in older people, including the type and mechanism of the interaction, potential harm and management (Table 2 and Appendix 5). The list includes 30 pharmacokinetic DDIs, 24 pharmacodynamic DDIs, 9 DDIs that are both pharmacokinetic and pharmacodynamic in nature and 3 DDIs for which the mechanism is not fully understood. Most DDIs concern antithrombotic agents, cardiovascular system drugs, central nervous system drugs and drugs with a narrow therapeutic index (e.g. digoxin). In terms of DDI management, treatment modification (i.e. dose reduction, discontinuation, substitution, adding a protective drug) is recommended for almost three-quarters of DDIs (48/66) and monitoring (e.g. electrolytes, blood pressure) is recommended for one quarter (18/66). Appendix 6 includes two summary tables of DDIs, per medication class and per type of adverse event.

## DISCUSSION

To our knowledge, this is the first list of potentially clinically significant DDIs in patients aged ≥65 years validated using an international Delphi panel. Consensus was achieved on 66 DDIs. The DDI list provides detailed information on the mechanism, potential harm and management of DDIs. Similar to explicit tools to detect potentially inappropriate prescribing in older people, the DDI list can be used to educate and assist healthcare professionals to detect potentially clinically significant DDIs. The DDI list could also be used to determine the prevalence of DDIs in epidemiological and intervention studies, as requested by recent core outcome sets.[8,9]

Most DDIs included in the DDI list concern antithrombotic agents, cardiovascular system drugs and central nervous system drugs causing severe potential harm such as bleeding, electrolyte disorders, serotonin syndrome etc. Although most of the medications involved are not considered potentially inappropriate when taken in isolation, DDIs with these medication classes have been shown to be among the most prevalent DDIs in both hospitalised and community-dwelling older people.[6,18,19] Hanlon et al. showed that 24%, 9% and 2% of older adults had a potential DDI involving cardiovascular medications, antithrombotic agents and central nervous system drugs, respectively.[18] Becker et al. found that most admissions related to DDIs were bleeding events (mostly involving NSAIDs, anticoagulants and corticosteroids), hyper- or hypotension, cardiac rhythm disturbances (mostly involving diuretics, glycosides, calcium channel blockers).[5] Juurlink et al. demonstrated that patients admitted with digoxin toxicity were 12 times more likely to have been co-prescribed clarithromycin and that patients on ACE-inhibitors admitted with hyperkalaemia were 20 times more likely to have been prescribed a potassium-sparing diuretic.[7] Our DDI list encompasses these situations and also includes some DDIs that either involve medications taken mostly by older people (e.g. DDI-57) or that might lead to geriatric syndromes (e.g. DDI-36). Several drugs included in the list are no longer or very rarely used in Europe (e.g. disopyramide, theophylline,

cimetidine). We asked panellists to avoid taking into account in their ratings the frequency of use of the drug in practice. As these drugs are still available on the international market and clinicians may be less aware of these DDIs because of infrequent use, we believe it is relevant to have included them.

Two lists of potentially serious DDIs in older people have been previously described, yet neither of them has been fully validated.[18,20] Furthermore, nine explicit tools designed to screen for inappropriate prescribing were identified from our literature review.[16,21-28] However, usually only a small proportion of the criteria is dedicated to DDIs and most lack information on the management of DDIs.[16,21-28] Incorporation of information on the mechanism, potential harm and the management of DDIs, enhances the clinical relevance of our tool. The DDI list is not intended to identify all potential DDIs in a given patient, but rather to call attention to drug combinations that are commonly problematic in older adults. Its use is different but complementary to that of specific DDI resources, which can be used for fully detailed information on the evidence and management of these DDIs, and to identify additional potential DDIs in individual patients. The explicit nature of the DDI list allows for easy implementation in clinical decision support systems and can be used to support communication with prescribers at dispensing, but it does not replace the more comprehensive electronic systems detecting an unrestricted number of DDIs. Table 3 lists six key principles to guide optimal use of the DDI list by clinicians.

Future perspectives include determining the prevalence of DDIs in different populations, and investigating the association with clinical outcomes such as drug-related hospitalisations. An algorithm based on the ATC codes of the 66 DDIs is available via https://github.com/agapiospanos/DDI.

Strengths and limitations

The DDI list was developed combining evidence from the literature and the Delphi method. We scrutinised drug interaction compendia to expand the list of DDIs with practical information on management of the

DDIs. A major limitation of this work is that the literature review was not systematic, ended at March 2018, used only PubMed to identify explicit DDI lists for older people and did not include a grading of the evidence base behind each DDI. Explicit DDI lists developed for the adult population in general were not considered.[29] The 2019 version of the AGS Beers criteria was published after our literature review and lists 17 potentially clinically important DDIs that should be avoided in older adults.[30] Thirteen are part of our final DDI list. Two DDIs are not included (i.e., phenytoin-TMP/SMX and peripheral $\alpha$-1 blockers-loop diuretics), and a final two are partially covered (i.e., opioids-benzodiazepines and opioids-gabapentin, pregabalin). These should be considered for inclusion in a future version, together with individual DDIs examined in pharmacoepidemiologic studies.

Selection of participants is the most important step of a Delphi study.[17] Hence, inclusion of a large international, multidisciplinary expert panel is a strength of our study. Some Delphi panellists reported having difficulties with rating the clinical relevance of a DDI without taking into account the likelihood of the DDI or preventive interventions, as requested in the survey instructions. There might have been different ways of scoring the DDIs in the Delphi survey. However, it was a deliberate choice to only score the severity of the DDI since our primary aim was to establish a list of clinically significant DDIs, regardless of the likelihood of the interaction.

Screening for all aspects of inappropriate prescribing as well as implicit patient-centred approaches remain key to medicines optimisation in older people.[32]

## CONCLUSIONS AND IMPLICATIONS

We developed a tool for detection of potentially clinically significant DDIs in older people, based on evidence from the literature and consensus agreement among an international, multidisciplinary Delphi panel. The 66-item DDI list can be used to assist healthcare professionals to detect potentially clinically significant DDIs in older people or to assess the prevalence of these DDIs in epidemiological and

intervention studies. Evaluation of the performance of the DDI list in terms of its association with clinical outcomes and identification of associated factors will be useful to further refine the list.

## CONFLICT OF INTEREST

There are no competing interests to declare.

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**Table 1.** Lists of DDIs identified from the literature review

| | Number of DDIs | Development method | Setting |
|---|---|---|---|
| **Existing list of DDIs** | | | |
| Hanlon et al. 2017 [18] | 31 | Literature search | Community |
| Mimica Matanovic et al 2012. [20] | 70 | Literature search | Not specified |
| **Explicit tools to detect inappropriate prescribing in older people and including DDIs** | | | |
| The AGS 2015 Beers criteria [21] | 13 | Delphi method | Not specified |
| The GheOP³S-tool (2015) [22] | 29 | RAND/UCLA method | Community |
| STOPP v2 (2015) [16] | 8 | Delphi method | Not specified |
| Laroche criteria (2007) [23] | 3 | Delphi method | Not specified |
| NORGEP (2009) [24] | 15 | Delphi method | Community |
| NORGEP-NH (2015) [25] | 15 | Delphi method | Long-term care |
| Rancourt (2004) [27] | 35 | Delphi method | Long-term care |
| Winit-Watjana (2008) [26] | 12 | Delphi method | Not specified |
| Top 10 Particularly dangerous drug interactions (2018) [28] | 10 | Expert panel | Long-term care |

DDIs: drug-drug interactions

**Table 2.** Final list of potentially clinically significant drug-drug interactions in older people (*n*=66)*

| DDI-number | Drug-drug interaction pairs | Type of DDI† | Potential harm | Management |
|---|---|---|---|---|
| DDI-1 | digoxin + amiodarone | PK + PD | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Monitor serum digoxin levels closely and adjust dosage accordingly<br>- Advise patients to promptly report any signs of digoxin toxicity such as nausea, vomiting, anorexia, visual disturbances, slow pulse/bradycardia, or irregular heartbeat/arrhythmia<br>- DDI-1: Reduce the digoxin dosage by one-third to one-half<br>- DDI-2: Reduce the digoxin dosage by one-third to one-half<br>- DDI-4: Reduce the digoxin dosage by one-half<br>- DDI-5: Substitute with non-macrolide antibiotic or reduce digoxin dosage by one-third to one-half<br>- DDI-6: Closely monitor serum levels of digoxin, potassium and magnesium |
| DDI-2 | digoxin + verapamil or diltiazem | PK + PD | | |
| DDI-3 | digoxin + propafenone | Unknown | | |
| DDI-4 | digoxin + quinidine | PK | | |
| DDI-5 | digoxin + some macrolides (i.e. erythromycin or clarithromycin or azithromycin or roxithromycin or telithromycin) | PK | | |
| DDI-6 | digoxin + thiazide or loop diuretic | PD | | |
| DDI-7 | vitamin K antagonist + a fibrate | PK + PD | Bleeding | - Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness<br>- DDI-7: Reduce the vitamin K antagonist dosage by one-third to one-half<br>- DDI-8: Substitute with a non-interacting gastroprotective drug (e.g. PPI like pantoprazole or another $H_2$ antagonist)<br>- DDI-10: Reduce the vitamin K antagonist dosage by one-quarter to one-half |
| DDI-8 | vitamin K antagonist + cimetidine | PK | | |
| DDI-9 | vitamin K antagonist + metronidazole | PK | | |
| DDI-10 | vitamin K antagonist + amiodarone | PK | | |
| DDI-11 | oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor or direct thrombin inhibitor) + an oral NSAID | PD | Bleeding, gastrointestinal bleeding and toxicity (i.e. inflammation, ulceration and perforation) | - Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness<br>- DDI-11: Consider the addition of a PPI or H2 antagonist during treatment with NSAID |
| DDI-12 | oral anticoagulant + an antiplatelet drug (including aspirin) | PD | Bleeding | |
| DDI-13 | vitamin K antagonist + trimethoprim/sulfamethoxazole | PK + PD | Bleeding | - Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness<br>- DDI-13: Substitute with another antibiotic |
| DDI-14 | vitamin K antagonist + a quinolone | Unknown | | |
| DDI-15 | vitamin K antagonist + a macrolide | PK + PD | | |
| DDI-16 | dabigatran + a P-gp inhibitor (ketoconazole, itraconazole, verapamil, quinidine, amiodarone, dronedarone, ciclosporin, clarithromycin, erythromycin, ritonavir) | PK | Bleeding | - Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness<br>- Specific recommendations for management may differ depending on: presence of risk factors (including renal failure), indication, interacting drug. Refer to appropriate literature and SmPC.<br>- DDI-16: Not recommended with ketoconazole, itraconazole, ciclosporin, dronedarone, ritonavir. For other interacting drugs, use with caution and/or reduce dosage.<br>- DDI-17: Reduce dosage or use with caution. |
| DDI-17 | edoxaban + a P-gp inhibitor (same list as for DDI-16) | PK | | |
| DDI-18 | rivaroxaban + a P-gp inhibitor or a CYP3A4-inhibitor ‡ (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, | PK | | |

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| | diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, , clarithromycin, erythromycin, ritonavir) | | | - DDI-18: Not recommended with azoles, ritonavir, dronedarone. For other interacting drugs, avoid use or use with caution<br>- DDI-19: Not recommended with azoles, ritonavir. For other interacting drugs, avoid use, reduce dosage and/or use with caution |
| DDI-19 | apixaban + a P-gp inhibitor or a CYP3A4-inhibitor ‡ | PK | | |
| DDI-20 | antiplatelet drug (including aspirin) + oral NSAID | PD | Bleeding, gastrointestinal toxicity (inflammation, ulceration, perforation)<br>Decreased cardioprotective effect with aspirin | - Consider the addition of gastroprotective drugs (e.g. PPI)<br>- Advise patients to promptly report any signs of ulceration and bleeding such as abdominal pain, bloating, sudden dizziness or light-headedness, nausea, vomiting, hematemesis, anorexia, and melena<br>- In order to preserve the cardioprotective effect of low-dose aspirin, administer the latter at least 2 hours before or at least 8h after NSAID intake |
| DDI-21 | concomitant use of ≥ 2 potassium-sparing drugs (i.e. amiloride, triamterene, eplerenone, spironolactone, ACE inhibitors, ARBs, NSAIDs, trimethoprim/sulfamethoxazole) | PD | Hyperkalaemia | - Closely monitor patients for serum potassium levels and renal function<br>- Educate patients about the potential danger of excessive potassium in the diet and advise them to promptly report any signs of hyperkalaemia such as nausea, vomiting, weakness, listlessness, tingling of the extremities, paralysis, confusion, weak pulse, and a slow or irregular heartbeat<br>- DDI-21: Extra caution is required in patients with moderate renal impairment, diabetes, severe or worsening heart failure, dehydration, or concomitant therapy with other agents that increase serum potassium such as beta-blockers, ciclosporine, heparin, tacrolimus, and trimethoprim. Avoid concurrent use in patients with severe renal impairment (CrCl < 30 ml/min) |
| DDI-22 | ACE inhibitor or ARB or a potassium-sparing diuretic + a potassium supplement | PD | | |
| DDI-23 | ACE inhibitor or ARB + an oral NSAID | PD | Deterioration of renal function and hyperkalaemia<br>Altered blood pressure control | - Keep the use of NSAIDs to a minimum in patients on antihypertensives, especially in those with blood pressures that are relatively high, as well as in those with high salt intake<br>- Monitor patient for altered blood pressure control and for renal function<br>- Ensure adequate hydration, avoiding dehydration or fluid overload |
| DDI-24 | diuretic + oral NSAID | PD | Deterioration of renal function, hyperkalaemia and congestive heart failure<br>Altered blood pressure control | - Keep the use of NSAID to a minimum in patients taking diuretics, especially in those with blood pressures that are relatively high, as well as in those with high salt intake or with congestive heart failure<br>- Monitor patients for signs of worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure<br>- Ensure adequate hydration, avoiding dehydration or fluid overload |
| DDI-25 | statin + gemfibrozil | PK | Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death | - Discontinue statin therapy if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is otherwise suspected or diagnosed<br>- Advise patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by fever, malaise, dark-coloured urine |
| DDI-26 | atorvastatin or simvastatin or lovastatin + verapamil or diltiazem | PK | | |

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| DDI-27 | simvastatin + amlodipine | PK | | - DDI-25: Contraindicated in a number of conditions considered to be risk factors for myopathy (i.e. renal impairment, hypothyroidism). Reduce the statin dosage to the lowest effective dose and consider using a fibrate other than gemfibrozil. If maintained, gemfibrozil dosage should not exceed 10mg daily<br>- DDI-26,27, 28: Consider safer alternatives not metabolized by CYP3A4 (e.g. fluvastatin, pravastatin or rosuvastatin).<br>- DDI-26,27, 28, 29: Reduce the dosage of involved statins to the lowest effective dose –do not exceed 20mg simvastatin and 40mg lovastatin daily<br>- DDI-29: Substitute with a non-interacting antibiotic or temporarily withdraw the statin as long as macrolide antibiotics are required, except if benefits outweigh risks |
| DDI-28 | atorvastatin or simvastatin or lovastatin + amiodarone | PK | | |
| DDI-29 | atorvastatin or simvastatin or lovastatin + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | | |
| DDI-30 | calcium channel blocker + a CYP3A4 inhibitor ‡ | PK | Increased effects of calcium channel blockers | - Monitor patients for cardiotoxicity (e.g. QT prolongation, torsade de pointes, bradycardia, congestive heart failure)<br>- Advise patients to promptly report any increased effects of calcium channels blockers such as headache, flushing, excessive hypotension, reflex tachycardia, oedema, difficulties breathing, chest pain or tightness |
| DDI-31 | disopyramide + some macrolides (i.e. erythromycin, clarithromycin telithromycin) | PK + PD | Hypoglycaemic coma, QT prolongation, torsade de pointes, heart block and ventricular fibrillation | - Avoid concurrent use except if benefits outweigh risks<br>- Substitute with non-macrolide antibiotic<br>- Closely monitor patients for cardiotoxicity<br>- Advise patients to promptly report any symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light-headedness, fainting, palpitations, irregular heartbeat, shortness of breath, or syncope |
| DDI-32 | beta-blocker + verapamil or diltiazem | PD | Potentially serious cardiovascular adverse effects including congestive heart failure, severe hypotension, exacerbation of angina, ventricular asystole, sinus arrest, heart block | - Avoid concurrent use, particularly in patients predisposed to heart failure<br>- Closely monitor patient hemodynamic response and tolerance and adjust the dosage of one or both agents accordingly<br>- Advise patients to promptly report any symptoms including fatigue, headache, fainting, swelling of the extremities, weight gain, shortness of breath, chest pain, increased or decreased heartbeat, or irregular heartbeat |
| DDI-33 | procainamide + amiodarone | PD | (Exacerbation of pre-existing) arrhythmias and QT prolongation | - Avoid concurrent use except for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or to amiodarone alone<br>- Reduce the dosage of both agents by one-third to one-half<br>- Monitor patients for conduction disturbances and exacerbation of tachyarrhythmia<br>- Advise patients to promptly report any symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light-headedness, fainting, palpitations, irregular heartbeat, shortness of breath, or syncope. |
| DDI-34 | procainamide + trimethoprim | PK | Cardiac adverse effects including QT prolongation, torsade | - Reduce the procainamide dosage. Monitor serum procainamide levels as well as patient response and adjust the procainamide dosage accordingly<br>- Patients should be advised to promptly report any signs of procainamide toxicity including drowsiness, dizziness, syncope, confusion, tremor or palpitations |

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| | | | de pointes, cardiac arrest | |
| DDI-35 | furosemide + etacrynic acid | PD | Ototoxicity with risk of tinnitus, reversible or irreversible hearing impairment, deafness | - Avoid concurrent use |
| DDI-36 | concomitant use of ≥ 3 centrally-acting drugs (i.e. opiates or antipsychotics or benzodiazepines/z-drugs or barbiturates or antiepileptics or antidepressants) | PD | Increased risk of falls and fracture, impaired cognition | - Minimise the number of CNS agents<br>- Limit the dosage and duration of each drug to the minimum possible while achieving the desired clinical effect<br>- Closely monitor patients for adverse effects |
| DDI-37 | alprazolam or diazepam or midazolam or triazolam or zolpidem or zopiclone + a CYP3A4 inhibitor ‡ | PK | Excessive sedation and prolonged hypnotic effects | - Consider benzodiazepine/Z-drug dosage reduction<br>- Advise patients to promptly report any symptoms of nausea, vomiting, diarrhoea, confusion, daytime sedation, dizziness or unconsciousness |
| DDI-38 | SSRI + another serotonergic drug (including tramadol) | PD<br><br>With tramadol: PD + PK | Serotonin syndrome<br>With tramadol: seizures and diminished therapeutic response to tramadol | - Closely monitor for symptoms of the serotonin syndrome such as hypertension, tachycardia, hyperthermia, myoclonus, mental status changes, particularly when initiating or increasing dosages of these agents. Consider potential risk even when administering serotonergic agents sequentially, as some of them may demonstrate prolonged elimination half-life (e.g. fluoxetine)<br>- With tramadol, use with caution regarding increased risk of seizure and monitor patient's therapeutic response<br>- When discontinuing a serotonergic CYP2D6 inhibitor in a patient receiving tramadol therapy, consider a tramadol dose reduction and monitor for signs of respiratory depression or sedation |
| DDI-39 | oral NSAID + SSRI or SNRIs | PD | Bleeding, gastrointestinal bleeding | - Substitute with alternatives to NSAIDs (e.g. paracetamol) or less gastrotoxic NSAIDs (e.g. ibuprofen)<br>- Consider the addition of gastroprotective drugs (e.g. PPI, $H_2$ antagonists)<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-40 | fluoxetine + tricyclic antidepressant | PD + PK | Serotonin syndrome<br>Tricyclic antidepressant toxicity, including cardiac arrhythmias | - Consider tricyclic antidepressant dosage reduction and serum level monitoring, even several weeks after fluoxetine discontinuation<br>- Closely monitor patients for signs of tricyclic antidepressants toxicity (e.g. cardiac arrhythmias, sedation, dry mouth, blurred vision, constipation, urinary retention) and/or excessive serotonergic activity (e.g. CNS irritability, altered consciousness, confusion, myoclonus, ataxia, abdominal cramping, hyperpyrexia, shivering, pupillary dilation, diaphoresis, hypertension, and tachycardia)<br>- If serotonin syndrome occurs, immediately discontinue fluoxetine and tricyclic antidepressants<br>- If ventricular arrhythmias develop, consider fluoxetine discontinuation and cardiac evaluation |
| DDI-41 | lithium + NSAID | PK | Lithium toxicity, potentially life-threatening | - Extra caution is advised in a number of conditions including advanced age, impaired renal function, decreased sodium intake, volume depletion, renal artery stenosis, and heart failure as these increase the risk of toxicity.<br>- Reduce the lithium dosage, titrate slowly and frequently monitor serum concentrations |
| DDI-42 | lithium + diuretic | PK | | |

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| DDI-43 | lithium + ACE inhibitor or an ARB | PK | | - Closely monitor patients for signs of lithium toxicity including drowsiness, dizziness, confusion, weakness, ataxia, tremor, tinnitus, blurred vision, nystagmus, vomiting, diarrhoea, thirst, diabetes insipidus (polyuria, polydipsia), seizure and ECG changes<br>- Advise patients to promptly report any signs of lithium toxicity (*listed above*) |
| DDI-44 | MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + sympathomimetic | PD | Hypertensive crisis | - DDI-44: Concurrent use is contraindicated. Wait at least 14 days after MAO inhibitor discontinuation before starting sympathomimetic use<br>- DDI-45: Avoid concurrent use even if carbidopa or benserazide are given in combination with levodopa. Wait two to three weeks after MAO-A inhibitor discontinuation before starting levodopa treatment |
| DDI-45 | MAO-A inhibitor (i.e. moclobemide) or non-selective MAO inhibitor (i.e. phenelzine or linezolid) + levodopa | PD | | |
| DDI-46 | MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + some opioids (i.e. meperidine or fentanyl) | PD | Serotonin syndrome<br>Respiratory depression, cyanosis, hypotension and coma | - Concurrent use is contraindicated or not recommended<br>- Wait at least 14 days after MAO inhibitor discontinuation before starting an opioid |
| DDI-47 | MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + an antidepressant (particularly a SSRI) | PD | Serotonin syndrome | - Concurrent use is contraindicated<br>- Wait at least 14 days between stopping a MAO inhibitor and starting another antidepressant; wait at least 7 to 14 days between stopping another antidepressant and starting a MAO inhibitor (5 weeks with fluoxetine)<br>- Monitor patients for signs of serotonin syndrome (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes) |
| DDI-48 | carbamazepine + verapamil or diltiazem | PK | Carbamazepine toxicity<br>Decreased therapeutic effect of verapamil, diltiazem, macrolide | - Closely monitor serum levels of carbamazepine and adjust the dosage accordingly<br>- Advise patients to promptly report any signs of carbamazepine toxicity such as headache, nausea, vomiting, dizziness, confusion, slurred speech, nystagmus, visual disturbances, tremors and ataxia<br>- DDI-48: Reduce carbamazepine dosage by one-half upon initiation of verapamil or diltiazem. Monitor blood pressure and cardiac effect after initiating carbamazepine<br>- DDI-49: Substitute with a non-macrolide antibiotic therapy or wait at least two weeks of discontinuing carbamazepine before using a macrolide. If co-administered, monitor patients for antimicrobial efficacy |
| DDI-49 | carbamazepine + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | | |
| DDI-50 | acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem) | PD | Bradycardia | - Use with caution, particularly in patients with increased risk of developing cardiac conduction disturbances<br>- Advise patients to promptly report any symptoms such as dizziness, light-headedness, fainting or irregular heartbeat |
| DDI-51 | theophylline + cimetidine | PK | Theophylline toxicity | - Closely monitor the theophylline serum levels and adjust the dosage accordingly<br>- Advise patients to promptly report any signs of theophylline toxicity such as nausea, vomiting, diarrhoea, headache, seizures, restlessness, insomnia, or irregular heartbeat/palpitations<br>- DDI-54: Substitute with other SSRI or reduce the theophylline dosage by one-third and closely monitor serum theophylline levels |
| DDI-52 | theophylline + a quinolone | PK | | |
| DDI-53 | theophylline + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | | |
| DDI-54 | theophylline + fluvoxamine | PK | | |
| DDI-55 | thiopurines (e.g. azathioprine) + allopurinol | PK | Azathioprine toxicity | - Reduce the azathioprine dosage by one-quarter to one-third<br>- Closely monitor patients for hematologic toxicity (leukopenia, thrombocytopenia, anaemia) |

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| | | | | - Advise patients to report any signs of thiopurine toxicity such as fever, chills, sore throat, fatigue, lethargy, pallor, anorexia, jaundice, dark urine, nausea, vomiting, signs of local infection and unusual bleeding or bruising |
| DDI-56 | oral or parenteral corticosteroid + an oral NSAID | PD | Gastrointestinal ulceration or bleeding | - Consider the addition of gastroprotective drugs (e.g. PPI, $H_2$ antagonists)<br>- Advise patients to report any signs of gastrointestinal ulceration and bleeding such as severe abdominal pain, dizziness, light-headedness and the appearance of black, tarry stools |
| DDI-57 | concomitant prescription of ≥ 2 anticholinergic drugs | PD | Anticholinergic effects including cognitive decline | - Minimise the number of anticholinergic drugs and consider non-anticholinergic alternatives<br>- Closely monitor patients for additive anticholinergic effects such as mydriasis, blurred vision, flushed face, fever, dry skin and mucous membranes, tachycardia, urinary retention, constipation, memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy and seizures<br>- Advise patients to promptly report any potential signs of anticholinergic effects such as abdominal pain, fever, heat intolerance, blurred vision, confusion or hallucinations |
| DDI-58 | ciclosporin + rifampicin | PK | Organ rejection | - Monitor serum levels of the immunosuppressant and adjust the dosage accordingly<br>- Monitor patient for signs of organ rejection |
| DDI-59 | ergot alkaloid (e.g. ergotamine) + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | Ergot toxicity | - Concurrent use is contraindicated given the potential for ergot toxicity characterised by nausea, vomiting, peripheral vasospasm, ischemia, thrombosis, tachycardia and hypertension |
| DDI-60 | methotrexate + trimethoprim | PD + PK | Potentially fatal methotrexate toxicity | - Closely monitor patients for hematologic toxicity (e.g. myelosuppression, pancytopenia, megaloblastic anaemic, severe bone marrow depression)<br>- Advise patients to promptly report any signs and symptoms of bone marrow depression or anaemia such as fever, chills, sore throat, easy bruising or bleeding, pallor, dizziness, fatigue, lethargy, sore mouth or tongue and tingling in hands or feet |
| DDI-61 | phosphodiesterase type 5-inhibitor + nitrate | PD | Severe hypotension, myocardial ischemia | - Concomitant use is contraindicated<br>- The time after when nitrates can be safely administered following PDE5 inhibitors use is uncertain and could go as far as 48 hours. Even then, closely monitor patients for hemodynamic response |
| DDI-62 | tamoxifen + vitamin K antagonist | Unknown | Bleeding | - Concomitant use is contraindicated<br>- Consider using lower doses of vitamin K antagonist and closely monitor the INR |
| DDI-63 | tamoxifen + citalopram or escitalopram | PD | Ventricular arrhythmias, torsade de pointes and sudden death | - Closely monitor patients for ECG changes<br>- Advise patients to promptly report any signs of toxicity such as drowsiness, dizziness, fainting/syncope, confusion or palpitations |
| DDI-64 | tamoxifen + paroxetine or fluoxetine or bupropion | PK | Reduced effectiveness of tamoxifen | - Consider other antidepressant with a limited impact in CYP2D6 activity or, eventually, aromatase inhibitors as tamoxifen substitutes |
| DDI-65 | concomitant prescription of ≥ 2 drugs that reduce potassium (e.g. β2-agonists, thiazides, loop diuretics, corticosteroids) | PD | Hypokalaemia, QT prolongation and torsade de pointes | - Closely monitor serum potassium levels<br>- Advise patients to promptly report any signs of hypokalaemia such as fatigue, weakness, myalgia, muscle cramps, numbness, tingling, abdominal pain, constipation, palpitation, and irregular heartbeat. |

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|---|---|---|---|---|
| DDI-66 | SSRI + loop or thiazide diuretic | PD | Hyponatraemia, orthostatic hypotension | - Closely monitor patients' sodium levels, blood pressure and pulse<br>- Advise patient to avoid rising abruptly from a sitting or recumbent position and to promptly report any signs of hyponatraemia including nausea, vomiting, headache, confusion, lethargy, weakness |

ACE: angiotensin-converting enzyme; ARB: angiotensin II type 1 receptor blockers; CNS: central nervous system; CrCl: creatinine clearance; CYP: cytochrome P450; DDI: drug-drug interaction; ECG: electrocardiogram; H2: histamine-2-receptor; INR: International Normalised Ratio; MAO: Monoamine oxidase; NSAID: non-steroidal anti-inflammatory drug; OATP: organic anion transporting polypeptide; PD: pharmacodynamic; PDE5: phosphodiesterase type 5; PK: pharmacokinetic; P-gp: P-glycoprotein; PPI: proton pump inhibitor; SmPC: Summary of product characteristics; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

* For key principles to guide optimal use of the DDI list by clinicians, please refer to Table 3.

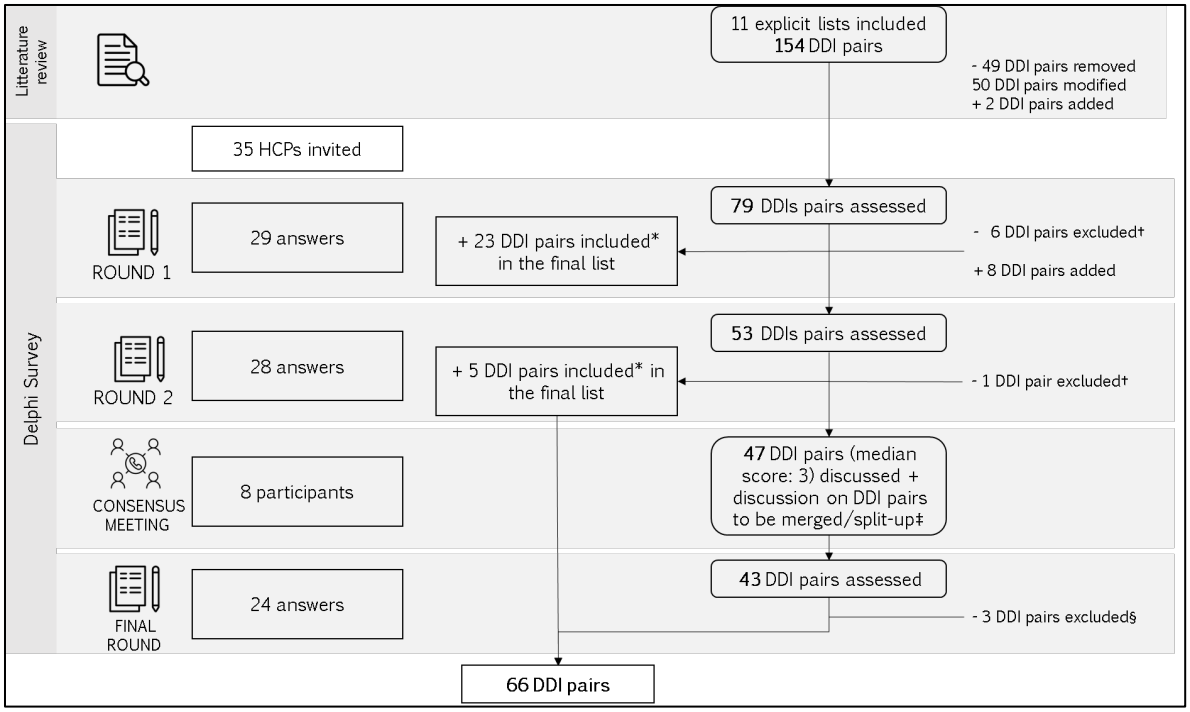
† Additional data on the mechanism of interaction are provided In Appendix 5. Pharmacodynamic DDIs occur between drugs with additive or opposing effects. They can be anticipated based on knowledge of the clinical effects of the drugs involved (mode of action, organs affected in relation to action or side effects). Pharmacokinetic DDIs cannot be predicted from the clinical effects of the drugs involved. They require knowledge on the PK parameters (absorption, distribution, metabolism and elimination) of each drug, and these parameters may vary between drugs of the same pharmacological class.

‡ CYP3A4 inhibitors include ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, ritonavir, clarithromycin, erythromycin

**Table 3.** Key principles to guide optimal use of the DDI list (table 2) by clinicians

- DDIs are *potentially* clinically significant, not *definitely* clinically significant
- The DDI list is not intended to identify all potential DDIs in a given patient, but rather to call attention to drug combinations that are commonly problematic in older adults.
- The DDI list should be a starting point for a comprehensive process of identifying DDIs and improving safety
- Read the suggestions for management in the DDI table. They will help to identify some factors that may increase the risks for specific patients
- For fully detailed information on the evidence and management of these DDIs, use specific and recognised DDI resources
- The explicit nature of the DDI list allows for easy implementation in clinical decision support systems, but does not replace more comprehensive electronic systems detecting an unrestricted number of DDIs.

**Appendix 1**. Flowchart of participants and DDI pairs in the Delphi study




Abbreviations: DDI: drug-drug interaction; HCP: healthcare professionals
* DDI pair with a median score of ≥4 and P25 ≥3 were directly included in the final list of DDIs
† DDIs with a median score of <3 were directly excluded
‡ Merging and splitting-up DDI pairs was also performed for the 28 DDIs directly included in rounds 1 and 2, resulting in 23 DDI pairs
§ A DDI pair was included in the final list if ≥ 75% of participants rated it « Yes »

**Appendix 2a**: Median [P25-P75] scores obtained for thedrug-drug interactions pairs evaluated in Delphi Round I (n=74)

| Drug-drug interaction pairs | Median score | P25 | P75 | Decision |
|---|---|---|---|---|
| Digoxin + amiodarone | 4 | 3 | 4 | Included |
| Digoxin + verapamil | 4 | 3 | 4 | Included |
| Digoxin + diltiazem | 3,5 | 3 | 4 | Round 2 |
| Digoxin + propafenone | 3 | 3 | 4 | Round 2 |
| Digoxin + quinidine | 3,5 | 3 | 4 | Round 2 |
| Digoxin + macrolides | 3 | 3 | 4 | Round 2 |
| Digoxin + thiazide diuretic | 3 | 2 | 3 | Round 2 |
| Vitamin K antagonist + fibrate | 3 | 2 | 3,5 | Round 2 |
| Vitamin K antagonist + cimetidine | 3 | 2 | 3,25 | Round 2 |
| Vitamin K antagonist + metronidazole | 3 | 2 | 3 | Round 2 |
| Vitamin K antagonist + amiodarone | 3 | 3 | 3 | Round 2 |
| Oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor or direct thrombin inhibitor) + oral NSAID | 4 | 3 | 4 | Included |
| Oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor or direct thrombin inhibitor) + antiplatelet drug (including aspirin) | 4 | 3 | 4 | Included |
| Vitamin K antagonist + trimethoprim/sulfamethoxazole | 3 | 3 | 4 | Round 2 |
| Vitamin K antagonist + quinolone | 3 | 2 | 3 | Round 2 |
| Vitamin K antagonist + macrolide | 3 | 3 | 4 | Round 2 |
| Vitamin K antagonist + thyroid hormone | 2 | 2 | 3 | Excluded |
| Vitamin K antagonist + SSRI | 2,5 | 2 | 3 | Excluded |
| Vitamin K antagonist + SNRI (i.e. venlafaxine, duloxetine) | 2 | 2 | 3 | Excluded |
| Dabigatran/edoxaban + P-gp inhibitor (ketoconazole, itraconazole, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, clarithromycin, erythromycin, ritonavir) | 4 | 3 | 4 | Included |
| Rivaroxaban/apixaban + P-gp inhibitor or a CYP3A4-inhibitor (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, ritonavir, clarithromycin, erythromycin) | 4 | 3 | 4 | Included |
| Oral NSAID + antiplatelet drug (including aspirin) | 3 | 3 | 4 | Round 2 |
| Clopidogrel + PPIs ((es)omeprazole, rabeprazole, lansoprazole) | 2 | 2 | 3 | Excluded |
| Concomitant use of ≥ 2 potassium-conserving drugs (i.e. amiloride, triamterene, eplerenone, spironolactone, ACE inhibitors, ARBs, NSAIDs, trimethoprim/sulfamethoxazole) | 3,5 | 3 | 5 | Round 2 |
| ACE inhibitor / ARB + potassium supplement | 3 | 3 | 4 | Round 2 |
| Potassium-sparing diuretic + potassium supplement | 3 | 3 | 4 | Round 2 |
| ACE inhibitor / ARB + oral NSAID | 3 | 3 | 3 | Round 2 |
| Antihypertensive + oral NSAID | 3 | 2 | 3 | Round 2 |
| Oral NSAID + diuretic | 3 | 3 | 3 | Round 2 |
| Statin, all + gemfibrozil | 3 | 2,75 | 4 | Round 2 |
| Atorvastatin / simvastatin / lovastatin + verapamil or diltiazem | 3 | 2 | 3 | Round 2 |
| Atorvastatin / simvastatin / lovastatin + amiodarone | 3 | 2 | 3 | Round 2 |

| | | | | |
|---|---|---|---|---|
| Atorvastatin / simvastatin / lovastatin + erythromycin/ clarithromycin / roxithromycin / telithromycin | 3 | 3 | 4 | Round 2 |
| Statin + azithromycin | 2 | 2 | 3 | Excluded |
| Calcium channel blocker + CYP3A4 inhibitor | 3 | 3 | 4 | Round 2 |
| Disopyramide + some macrolides (i.e. erythromycin, clarithromycin, telithromycin) | 4 | 3 | 5 | Included |
| Beta-blocker + verapamil or diltiazem | 4 | 3 | 4 | Included |
| Procainamide + amiodarone | 4 | 3 | 5 | Included |
| Procainamide + trimethoprim | 3 | 3 | 4 | Round 2 |
| Furosemide + etacrynic acid | 3 | 2 | 4 | Round 2 |
| Concomitant use of ≥ 3 centrally-acting drugs (i.e. opiates or antipsychotics or benzodiazepines/z-drugs or barbiturates or antiepileptics or antidepressants or anti-dementia drugs or psychostimulants) | 4 | 3 | 4 | Included |
| Alprazolam or diazepam or midazolam or triazolam or zolpidem or zopiclone + a CYP3A4 inhibitor | 3 | 2 | 4 | Round 2 |
| Tricyclic antidepressant + clonidine | 3 | 2 | 3 | Round 2 |
| SSRI + metoclopramide | 3 | 2 | 4 | Round 2 |
| SSRI + another serotoninergic drug (including tramadol) | 3 | 3 | 3 | Round 2 |
| SSRI + MAO inhibitors (i.e. selegiline, rasagiline, safinamide phenelzine, moclobemide) | 4 | 3,75 | 4 | Included |
| Oral NSAID + SSRI | 3 | 2,75 | 4 | Round 2 |
| Oral NSAID + SNRI | 3 | 2 | 3 | Round 2 |
| Fluoxetine + tricyclic antidepressant | 4 | 3 | 4 | Included |
| Lithium + (oral) NSAID | 3 | 3 | 4 | Round 2 |
| Lithium + a diuretic | 4 | 3 | 4 | Included |
| Lithium + ACE inhibitor or ARB | 3 | 3 | 4 | Round 2 |
| MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + a sympathomimetic drug | 4 | 3 | 4 | Included |
| MAO-A inhibitor (i.e. moclobemide) or a non-selective MAO inhibitor (i.e. phenelzine or linezolid) + levodopa | 4 | 3 | 4 | Included |
| MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + some opiates (i.e. meperidine or fentanyl or oxycodone) | 4 | 3 | 4 | Included |
| MAO inhibitors (i.e. Rasagiline, safinamide, selegiline, phenelzine, moclobemide) + antidepressants (e.g. trazodone, SSRI, SNRI, tricyclic antidepressant) | 4 | 3 | 4 | Included |
| Phenytoin + omeprazole | 2 | 2 | 3 | Excluded |
| Carbamazepine + verapamil | 3 | 2 | 3,25 | Round 2 |
| Carbamazepine + diltiazem | 3 | 2 | 4 | Round 2 |
| Carbamazepine + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 3 | 2,75 | 4 | Round 2 |
| Acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem) | 3 | 2,75 | 3 | Round 2 |
| Theophylline + cimetidine | 3 | 3 | 4 | Round 2 |
| Theophylline + quinolone | 3 | 3 | 4 | Round 2 |
| Theophylline + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 3 | 3 | 4 | Round 2 |
| Theophylline + fluvoxamine | 3 | 3 | 4 | Round 2 |
| Thiopurines (e.g. azathioprine) + allopurinol | 4 | 3 | 5 | Included |
| Oral or parenteral corticosteroids + oral NSAIDs | 3 | 3 | 4 | Round 2 |

| | | | | |
|---|---|---|---|---|
| Concomitant prescription of ≥ 2 anticholinergic drugs | 3 | 3 | 4 | Round 2 |
| Tamoxifen + fluoxetine | 4 | 3 | 4 | Included |
| Tamoxifen + paroxetine | 4 | 2,75 | 4 | Round 2 |
| Cyclosporine + rifampicin | 4 | 4 | 5 | Included |
| Ergot alkaloid + erythromycin, clarithromycin, roxithromycin, telithromycin | 4 | 3 | 4 | Included |
| Methotrexate + trimethoprim | 4 | 4 | 4,25 | Included |
| Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) + daily nitrate therapy for angina | 4 | 3 | 4 | Included |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blockers; CYP, cytochrome P450; MAO, Monoamine oxidase; NSAID, non-steroidal anti-inflammatory drug; P-gp, P-glycoprotein; PPI, proton pump inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

**Appendix 2b**: Median [P25-P75] scores obtained for the drug-drug interactions pairs evaluated in Delphi Round II (*n*=53)

| Drug-drug interaction pairs | Median score | P25 | P75 | Decision |
|---|---|---|---|---|
| Digoxin + verapamil or diltiazem | 4 | 3 | 4 | Included |
| Digoxin + propafenone | 3 | 3 | 4 | Consensus meeting |
| Digoxin + quinidine | 4 | 3 | 4 | Included |
| Digoxin + some macrolides (i.e. erythromycin or clarithromycin or azithromycin or roxithromycin or telithromycin) | 3 | 3 | 3,5 | Consensus meeting |
| Digoxin + thiazide diuretic | 3 | 3 | 3 | Consensus meeting |
| Vitamin K antagonist + fibrate | 3 | 3 | 3 | Consensus meeting |
| Vitamin K antagonist + cimetidine | 3 | 3 | 3 | Consensus meeting |
| Vitamin K antagonist + metronidazole | 3 | 3 | 3 | Consensus meeting |
| Vitamin K antagonist + amiodarone | 3 | 3 | 3,5 | Consensus meeting |
| Vitamin K antagonist + trimethoprim/sulfamethoxazole | 3 | 3 | 4 | Consensus meeting |
| Vitamin K antagonist + quinolone | 3 | 3 | 3 | Consensus meeting |
| Vitamin K antagonist + macrolide | 3 | 3 | 3 | Consensus meeting |
| Oral NSAID + antiplatelet drug (including aspirin) | 3 | 3 | 4 | Consensus meeting |
| Concomitant use of ≥ 2 potassium-conserving drugs (i.e. amiloride, triamterene, eplerenone, spironolactone, ACE inhibitors, ARBs, NSAIDs, trimethoprim/sulfamethoxazole) | 4 | 4 | 4,5 | Included |
| ACE inhibitor / ARB + potassium supplement | 3 | 3 | 4 | Consensus meeting |
| Potassium-sparing diuretic + potassium supplement | 3 | 3 | 4 | Consensus meeting |
| ACE inhibitor / ARB + oral NSAID | 3 | 3 | 3 | Consensus meeting |
| Antihypertensive + oral NSAID | 3 | 3 | 3 | Consensus meeting |
| Oral NSAID + diuretic | 3 | 3 | 3 | Consensus meeting |
| Statin, all + gemfibrozil | 3 | 3 | 4 | Consensus meeting |
| Atorvastatin / simvastatin / lovastatin + verapamil or diltiazem | 3 | 3 | 3 | Consensus meeting |
| Atorvastatin / simvastatin / lovastatin + amiodarone | 3 | 3 | 3 | Consensus meeting |
| Atorvastatin / simvastatin / lovastatin + erythromycin / clarithromycin / roxithromycin / telithromycin | 3 | 3 | 3 | Consensus meeting |
| Calcium channel blocker + CYP3A4 inhibitor | 3 | 3 | 3,5 | Consensus meeting |
| Procainamide + trimethoprim | 3 | 3 | 4 | Consensus meeting |
| Furosemide + ethacrynic acid | 3 | 3 | 4 | Consensus meeting |
| Alprazolam or diazepam or midazolam or triazolam or zolpidem or zopiclone + a CYP3A4 inhibitor | 3 | 3 | 3,5 | Consensus meeting |
| Tricyclic antidepressant + clonidine | 3 | 2 | 3 | Consensus meeting |
| SSRI + metoclopramide | 3 | 3 | 3,75 | Consensus meeting |
| SSRI + another serotoninergic drug (including tramadol) | 3 | 3 | 3 | Consensus meeting |
| Oral NSAID + SSRI | 3 | 3 | 3 | Consensus meeting |
| Oral NSAID + SNRI | 3 | 3 | 3 | Consensus meeting |
| Lithium + (oral) NSAID | 3 | 3 | 4 | Consensus meeting |
| Lithium + ACE inhibitor or ARB | 3 | 3 | 4 | Consensus meeting |
| Carbamazepine + verapamil | 3 | 3 | 3 | Consensus meeting |
| Carbamazepine + diltiazem | 3 | 3 | 3 | Consensus meeting |
| Carbamazepine + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 3 | 3 | 3 | Consensus meeting |

| | | | | |
|---|---|---|---|---|
| Acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem) | 3 | 3 | 3 | Consensus meeting |
| Theophylline + cimetidine | 3 | 3 | 3,5 | Consensus meeting |
| Theophylline + quinolone | 3 | 3 | 4 | Consensus meeting |
| Theophylline + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 3 | 3 | 4 | Consensus meeting |
| Theophylline + fluvoxamine | 3 | 3 | 4 | Consensus meeting |
| Oral or parenteral corticosteroids + oral NSAIDs | 3 | 3 | 3,5 | Consensus meeting |
| Concomitant prescription of ≥ 2 anticholinergic drugs | 3 | 3 | 3 | Consensus meeting |
| Tamoxifen + paroxetine / fluoxetine / sertraline | 4 | 3,5 | 4 | Included |
| Digoxin + loop diuretic[a] | 3 | 3 | 4 | Consensus meeting |
| Tamoxifen + warfarin[a] | 3 | 3 | 4 | Consensus meeting |
| Tamoxifen + (es)citalopram[a] | 3 | 3 | 3,5 | Consensus meeting |
| Tamoxifen + bupropion[a] | 4 | 3 | 4 | Included |
| Simvastatin + amlodipine[a] | 3 | 2 | 3 | Consensus meeting |
| Salbutamol + drugs that reduce potassium (e.g. loop or thiazide diuretics) [a] | 3 | 2 | 3 | Consensus meeting |
| SSRI + loop or thiazide diuretics[a] | 3 | 3 | 4 | Consensus meeting |
| Acetylcholinesterase inhibitor + anticholinergic drug[a] | 2 | 2 | 3 | Excluded |

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blockers; NSAID, non-steroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

[a]Drug-drug interactions added for evaluation at Round 2 after suggestions made by participants at Round 1.

**Appendix 3.** Answers of participants (N=24) for the drug-drug interaction pairs evaluated at final round

| **Drug-drug interaction pairs** (median score of 3 at round 2) | N | % | Decision* |
|---|---|---|---|
| digoxin + propafenone | 18 | 75 | Included |
| digoxin + some macrolides (i.e. erythromycin or clarithromycin or azithromycin or roxithromycin or telithromycin) | 23 | 96 | Included |
| digoxin + thiazide or loop diuretic | 19 | 79 | Included |
| vitamin K antagonist + a fibrate | 22 | 92 | Included |
| vitamin K antagonist + cimetidine | 18 | 75 | Included |
| vitamin K antagonist + metronidazole | 22 | 92 | Included |
| vitamin K antagonist + amiodarone | 23 | 96 | Included |
| vitamin K antagonist + trimethoprim/sulfamethoxazole | 22 | 92 | Included |
| vitamin K antagonist + a quinolone | 20 | 83 | Included |
| vitamin K antagonist + a macrolide | 21 | 88 | Included |
| antiplatelet drug (including aspirin) + oral NSAID | 21 | 88 | Included |
| ACE inhibitor or ARB or a potassium-sparing diuretic + a potassium supplement | 22 | 92 | Included |
| ACE inhibitor or ARB + an oral NSAID | 20 | 83 | Included |
| antihypertensive + oral NSAID | 14 | 58 | Excluded |
| diuretic + oral NSAID | 19 | 79 | Included |
| statin + gemfibrozil | 24 | 100 | Included |
| atorvastatin or simvastatin or lovastatin + verapamil or diltiazem | 22 | 92 | Included |
| simvastatin + amlodipine | 19 | 79 | Included |
| atorvastatin or simvastatin or lovastatin + amiodarone | 23 | 96 | Included |
| atorvastatin or simvastatin or lovastatin + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 22 | 92 | Included |
| calcium channel blocker + a CYP3A4 inhibitor | 20 | 83 | Included |
| procainamide + trimethoprim | 21 | 88 | Included |
| furosemide + etacrynic acid | 19 | 79 | Included |
| alprazolam or diazepam or midazolam or triazolam or zolpidem or zopiclone + a CYP3A4 inhibitor | 18 | 75 | Included |
| tricyclic antidepressant + clonidine | 14 | 58 | Excluded |
| SSRI + metoclopramide | 17 | 71 | Excluded |
| SSRI + another serotonergic drug (including tramadol) | 22 | 92 | Included |
| oral NSAID + SSRI or SNRIs | 19 | 79 | Included |
| lithium + NSAID | 24 | 100 | Included |
| lithium + ACE inhibitor or an ARB | 23 | 96 | Included |
| carbamazepine + verapamil or diltiazem | 20 | 83 | Included |
| carbamazepine + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 20 | 83 | Included |
| acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem) | 20 | 83 | Included |
| theophylline + cimetidine | 20 | 83 | Included |
| theophylline + a quinolone | 22 | 92 | Included |
| theophylline + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | 22 | 92 | Included |
| theophylline + fluvoxamine | 23 | 96 | Included |
| oral or parenteral corticosteroid + an oral NSAID | 24 | 100 | Included |
| concomitant prescription of ≥ 2 anticholinergic drugs | 22 | 92 | Included |

| | | | |
|---|---|---|---|
| tamoxifen + vitamin K antagonist | 21 | 88 | Included |
| tamoxifen + citalopram or escitalopram | 20 | 83 | Included |
| concomitant prescription of ≥ 2 drugs that reduce potassium | 19 | 79 | Included |
| SSRI + loop or thiazide diuretic | 19 | 79 | Included |

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blockers; NSAID, non-steroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

* A drug-drug interaction was included if ≥75% of participants rated it YES (i.e. should be included in the final list) in this final round

**Appendix 4.** Drug-drug interaction pairs excluded from the final list

- Vitamin K antagonist + thyroid hormone
- Vitamin K antagonist + SSRI
- Vitamin K antagonist + SNRI (i.e. venlafaxine, duloxetine)
- Clopidogrel + PPIs ((es)omeprazole, rabeprazole, lansoprazole)
- Statin + azithromycin
- Phenytoin + omeprazole
- Acetylcholinesterase inhibitor + anticholinergic drugs
- Antihypertensive + oral NSAID
- Tricyclic antidepressant + clonidine
- SSRI + metoclopramide

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

| **Appendix 5.** Final list of potentially clinically significant drug-drug interactions in older people (*n*=66)* | | | | | |
|---|---|---|---|---|---|
| **DDI-number** | **Drug-drug interaction pairs** | **Type of interaction†** | **Mechanism of interaction** | **Potential harm** | **Management** |
| DDI-1 | digoxin + amiodarone | PK + PD | - Increased digoxin exposure due to the inhibition of P-gp by amiodarone<br>- Additive bradycardia | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Reduce the digoxin dosage by one-third to one-half<br>- Monitor serum digoxin levels closely and adjust dosage accordingly<br>- Advise patients to promptly report any signs of digoxin toxicity such as nausea, vomiting, anorexia, visual disturbances, slow pulse/bradycardia, or irregular heartbeat/arrhythmia |
| DDI-2 | digoxin + verapamil or diltiazem | PK + PD | - Decreased digoxin clearance possibly relying, at least in the case of verapamil, on P-gp inhibition<br>- Additive effects in slowing atrioventricular node conduction | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Reduce the digoxin dosage by one-third to one-half<br>- Monitor serum digoxin levels closely and adjust dosage accordingly<br>- Advise patients to promptly report any signs of digoxin toxicity such as nausea, vomiting, anorexia, visual disturbances, slow pulse/bradycardia, or irregular heartbeat/arrhythmia. |
| DDI-3 | digoxin + propafenone | Unknown | *Not fully understood*<br>Propafenone may increase serum digoxin concentration | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Monitor serum digoxin levels closely and adjust dosage accordingly<br>- Advise patients to promptly report any signs of digoxin toxicity such as nausea, vomiting, anorexia, visual disturbances, slow pulse/bradycardia, or irregular heartbeat/arrhythmia |
| DDI-4 | digoxin + quinidine | PK | Increased digoxin exposure, possibly relying on P-gp inhibition by quinidine | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Reduce the digoxin dosage by one-half<br>- Monitor serum digoxin levels closely and adjust dosage accordingly<br>- Advise patients to promptly report any signs of digoxin toxicity such as nausea, vomiting, anorexia, visual disturbances, slow pulse/bradycardia, or irregular heartbeat/cardiac arrhythmias |
| DDI-5 | digoxin + some macrolides (i.e. erythromycin or clarithromycin or azithromycin or roxithromycin or telithromycin) | PK | Increased digoxin exposure due to the inhibition of P-gp by some macrolides | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Substitute with non-macrolide antibiotic or reduce digoxin dosage by one-third to one-half<br>- Monitor serum digoxin levels closely and adjust dosage accordingly<br>- Advise patients to promptly report any signs of digoxin toxicity such as nausea, vomiting, anorexia, visual disturbances, slow pulse/bradycardia, or irregular heartbeat/cardiac arrhythmias |

| | | | | | |
|---|---|---|---|---|---|
| DDI-6 | digoxin + thiazide or loop diuretic | PD | Potentiation of cardiac glycoside-mediated Na-K-ATPase inhibition due to the induction of hypokalaemia and hypomagnesaemia by diuretics | Digoxin toxicity, that may lead to potentially fatal cardiac arrhythmia | - Closely monitor serum levels of digoxin, potassium and magnesium<br>- Advise patients to promptly report any signs of digoxin toxicity or electrolyte disturbances such as weakness, lethargy, muscle pains or cramps, nausea, anorexia, visual changes, slow pulse/bradycardia, or irregular heartbeat/cardiac arrhythmias |
| DDI-7 | vitamin K antagonist + a fibrate | PK + PD | *Not fully understood*<br>- Protein binding displacement of vitamin K antagonists by fibrates<br>- Additive effects on anticoagulation | Bleeding | - Reduce the vitamin K antagonist dosage by one-third to one-half<br>- Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-8 | vitamin K antagonist + cimetidine | PK | Increased vitamin K antagonist exposure due to the inhibition of CYP1A2- and CYP2C19-mediated metabolisms by cimetidine | Bleeding | - Substitute with a non-interacting gastroprotective drug (e.g. PPI like pantoprazole or another $H_2$ antagonist)<br>- Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-9 | vitamin K antagonist + metronidazole | PK | Increased vitamin K antagonist exposure due to the inhibition CYP2C9-mediated metabolism by metronidazole | Bleeding | - Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-10 | vitamin K antagonist + amiodarone | PK | Increased vitamin K antagonist exposure due to the inhibition of CYP1A2-, CYP2C9-, CYP3A4-mediated metabolism by amiodarone | Bleeding | - Reduce the vitamin K antagonist dosage by one-quarter to one-half<br>- Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-11 | oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor | PD | Potentiation of the bleeding risk associated with oral anticoagulants due to additive | Bleeding, gastrointestinal bleeding and toxicity (i.e. | - Consider the addition of a PPI or H2 antagonist during treatment with NSAID |

| | | | | | |
|---|---|---|---|---|---|
| | or direct thrombin inhibitor) + an oral NSAID | | pharmacodynamic effects on haemostasis and gastrointestinal irritation or ucleration by NSAIDs | inflammation, ulceration and perforation) | - Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-12 | oral anticoagulant (i.e. vitamin K antagonist or factor Xa inhibitor or direct thrombin inhibitor) + an antiplatelet drug (including aspirin) | PD | Additive effects on haemostasis | Bleeding | - Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-13 | vitamin K antagonist + trimethoprim/sulfamethoxazole | PK + PD | - Increased vitamin K antagonist exposure due to the inhibition of CYP2C9-mediated metabolism by sulfamethoxazole<br>- Potentiation of the hypothrombinaemic effect of vitamin K antagonist through the disruption of vitamin K-producing intestinal flora by trimethoprim and sulfamethoxazole | Bleeding | - Substitute with another antibiotic<br>- Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-14 | vitamin K antagonist + a quinolone | Unknown | *Not fully understood*<br>Potentiation of the hypothrombinaemic effect of vitamin K antagonist through the disruption of vitamin K-producing intestinal flora by quinolones | Bleeding | - Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-15 | vitamin K antagonist + a macrolide | PK + PD | *Not fully understood*<br>- Potentiation of the hypothrombinaemic effect of vitamin K antagonist through the disruption of vitamin K-producing intestinal flora by macrolides<br>- Increased vitamin K antagonist exposure due to the inhibition of CYP3A4-mediated metabolism by macrolides | Bleeding | - Monitor the INR closely and adjust the vitamin K antagonist dosage accordingly<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |

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| DDI-16 | dabigatran + a P-gp inhibitor (ketoconazole, itraconazole, verapamil, quinidine, amiodarone, dronedarone, ciclosporin, clarithromycin, erythromycin, ritonavir) | PK | Increased exposure to dabigatran due to the inhibition of P-gp-mediated efflux transport | Bleeding | - Not recommended with ketoconazole, itraconazole, ciclosporin, dronedarone, ritonavir. For other interacting drugs, use with caution and/or reduce dosage.<br>- Specific recommendations for management may differ depending on: presence of risk factors (including renal failure), indication, interacting drug. Refer to appropriate literature and SmPC.<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-17 | edoxaban + a P-gp inhibitor (ketoconazole, itraconazole, verapamil, quinidine, amiodarone, dronedarone, ciclosporin, clarithromycin, erythromycin, ritonavir) | PK | Increased exposure to edoxaban due to the inhibition of P-gp-mediated efflux transport | Bleeding | - Reduce dosage or use with caution. Specific recommendations for management may differ depending on: presence of risk factors, indication, interacting drug. Refer to appropriate literature and SmPC.<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-18 | rivaroxaban + a P-gp inhibitor or a CYP3A4-inhibitor (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, , clarithromycin, erythromycin, ritonavir) | PK | Increased exposure to rivaroxaban due to the inhibition of P-gp and CYP3A4-mediated metabolism | Bleeding | - Not recommended with azoles, ritonavir, dronedarone. For other interacting drugs, avoid use or use with caution<br>- Specific recommendations for management may differ depending on: presence of risk factors (including renal failure), indication, interacting drug. Refer to appropriate literature and SmPC.<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-19 | apixaban + a P-gp inhibitor or a CYP3A4-inhibitor (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, clarithromycin, erythromycin ritonavir) | PK | Increased exposure to apixaban due to the inhibition of P-gp and CYP3A4-mediated metabolism | Bleeding | - Not recommended with azoles, ritonavir. For other interacting drugs, avoid use, reduce dosage and/or use with caution<br>- Specific recommendations for management may differ depending on: presence of risk factors (including renal failure), indication, interacting drug. Refer to appropriate literature and SmPC.<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-20 | antiplatelet drug (including aspirin) + oral NSAID | PD | - Potentiation of bleeding risk associated with oral anticoagulants due to additive pharmacodynamic effects on haemostasis and gastrointestinal irritation by NSAIDs<br>- Competition at the platelet cyclooxygenase-1 (COX-1) binding site between aspirin and other NSAIDs | - Bleeding, gastrointestinal bleeding and toxicity (i.e. inflammation, ulceration and perforation)<br>With aspirin, decreased cardioprotective effect | - Consider the addition of gastroprotective drugs (e.g. PPI)<br>- Advise patients to promptly report any signs of ulceration and bleeding such as abdominal pain, bloating, sudden dizziness or light-headedness, nausea, vomiting, hematemesis, anorexia, and melena<br>- In order to preserve the cardioprotective effect of low-dose aspirin, administer the latter at least 2 hours before or at least 8h after NSAID intake |
| DDI-21 | concomitant use of ≥ 2 potassium-sparing drugs (i.e. amiloride, triamterene, eplerenone, spironolactone, ACE inhibitors, ARBs, NSAIDs, trimethoprim/sulfamethoxazole) | PD | Additive effects resulting in potassium retention | Hyperkalaemia | - Extra caution is required in patients with moderate renal impairment, diabetes, severe or worsening heart failure, dehydration, or concomitant therapy with other agents that increase serum potassium such as beta-blockers, ciclosporine, heparin, tacrolimus, and trimethoprim. Avoid concurrent use in patients with severe renal impairment (CrCl < 30 ml/min)<br>- Closely monitor patients for serum potassium levels and renal function<br>- Educate patients about the potential danger of excessive potassium in the diet and advise them to promptly report any signs of hyperkalaemia such as nausea, vomiting, weakness, listlessness, tingling of the extremities, paralysis, confusion, weak pulse, and a slow or irregular heartbeat |
| DDI-22 | ACE inhibitor or ARB or a potassium-sparing diuretic + a potassium supplement | PD | Additive effects resulting in potassium retention | Hyperkalaemia | - Closely monitor serum potassium levels<br>- Educate patients about the potential danger of excessive potassium in the diet and advise them to promptly report any signs of hyperkalaemia such as nausea, vomiting, weakness, listlessness, tingling of the extremities, paralysis, confusion, weak pulse, and a slow or irregular heartbeat |
| DDI-23 | ACE inhibitor or ARB + an oral NSAID | PD | - Additive adverse effects on renal function<br>- Antagonist effects on blood pressure | - Deterioration of renal function and hyperkalaemia<br>Altered blood pressure control | - Keep the use of NSAIDs to a minimum in patients on antihypertensives, especially in those with blood pressures that are relatively high, as well as in those with high salt intake<br>- Monitor patient for altered blood pressure control and for renal function |

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| | | | | | - Ensure adequate hydration, avoiding dehydration or fluid overload |
| DDI-24 | diuretic + oral NSAID | PD | - Additive adverse effects on renal function<br>- Antagonist effects on salt/water retention and blood pressure | - Deterioration of renal function, hyperkalaemia and congestive heart failure<br>Altered blood pressure control | - Keep the use of NSAID to a minimum in patients taking diuretics, especially in those with blood pressures that are relatively high, as well as in those with high salt intake or with congestive heart failure<br>- Monitor patients for signs of worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure<br>- Ensure adequate hydration, avoiding dehydration or fluid overload |
| DDI-25 | statin + gemfibrozil | PK | Increased statin exposure due to gemfibrozil-mediated inhibition of the glucuronidation process and of the OATP1B1 transporter | Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death | - Contraindicated in a number of conditions considered to be risk factors for myopathy (i.e. renal impairment, hypothyroidism)<br>- Reduce the statin dosage to the lowest effective dose and consider using a fibrate other than gemfibrozil. If maintained, gemfibrozil dosage should not exceed 10mg daily<br>- Discontinue statin therapy if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is otherwise suspected or diagnosed<br>- Advise patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by fever, malaise and/or dark-coloured urine |
| DDI-26 | atorvastatin or simvastatin or lovastatin + verapamil or diltiazem | PK | Increased statin exposure due to the inhibition of CYP3A4-mediated metabolism by verapamil and diltiazem | Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death | - Consider safer alternatives not metabolized by CYP3A4 (e.g. fluvastatin, pravastatin or rosuvastatin)<br>- Reduce the dosage of involved statins to the lowest effective dose<br>- Discontinue statin if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is otherwise suspected or diagnosed<br>- Advise patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by fever, malaise and/or dark-coloured urine |
| DDI-27 | simvastatin + amlodipine | PK | *Not fully understood*<br>Substrate competition for CYP3A4-mediated metabolism | Severe myopathy and rhabdomyolysis which may lead to acute renal failure and death | - Consider safer alternatives not metabolized by CYP3A4 (e.g. fluvastatin, pravastatin or rosuvastatin)<br>- Reduce the statin dosage to the lowest effective dose and do not exceed 20mg simvastatin daily |

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| | | | | | - Discontinue statin if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is otherwise suspected or diagnosed<br>- Advise patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by fever, malaise and/or dark-coloured urine |
| DDI-28 | atorvastatin or simvastatin or lovastatin + amiodarone | PK | Increased statin exposure due to the inhibition of CYP3A4-mediated metabolism by amiodarone | Severe myopathy and rhabdomyolysis which may lead to acute renal failure | - Consider safer alternatives not metabolised by CYP3A4 (e.g. fluvastatin, pravastatin, rosuvastatin)<br>- Reduce the statin dosage to the lowest effective dose (not exceeding 20mg simvastatin and 40mg lovastatin daily)<br>- Discontinue statin if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is otherwise suspected or diagnosed<br>- Advise patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by fever, malaise and/or dark-coloured urine |
| DDI-29 | atorvastatin or simvastatin or lovastatin + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | Some macrolides inhibit CYP3A4-mediated metabolism, resulting in increased statin exposure | Severe myopathy and rhabdomyolysis which may lead to acute renal failure | - Substitute with a non-interacting antibiotic or temporarily withdraw the statin as long as macrolide antibiotics are required, except if benefits outweigh risks<br>- Reduce the statin dosage to the lowest effective dose<br>- Discontinue statin if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is otherwise suspected or diagnosed<br>- Advise patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by fever, malaise and/or dark-coloured urine |
| DDI-30 | calcium channel blocker + a CYP3A4 inhibitor (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, ritonavir, clarithromycin, erythromycin) | PK | Increased exposure to calcium channel blockers due the inhibition of CYP3A4-mediated metabolism | Increased effects of calcium channel blockers | - Monitor patients for cardiotoxicity (e.g. QT prolongation, torsade de pointes, bradycardia, congestive heart failure)<br>- Advise patients to promptly report any increased effects of calcium channels blockers such as headache, flushing, excessive hypotension, reflex tachycardia, oedema, difficulties breathing, chest pain or tightness |
| DDI-31 | disopyramide + some macrolides (i.e. erythromycin, clarithromycin telithromycin) | PK + PD | - Increased disopyramide exposure due to the inhibition | Hypoglycaemic coma, QT prolongation, torsade de | - Avoid concurrent use except if benefits outweigh risks<br>- Substitute with non-macrolide antibiotic<br>- Closely monitor patients for cardiotoxicity |

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| | | | of CYP3A4-mediated metabolism<br>- Additive effects on QT prolongation | pointes, heart block and ventricular fibrillation | - Advise patients to promptly report any symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light-headedness, fainting, palpitations, irregular heartbeat, shortness of breath, or syncope |
| DDI-32 | beta-blocker + verapamil or diltiazem | PD | Additive cardiac depressant effects with reduction in heart rate, atrioventricular conduction and cardiac contractility | Potentially serious cardiovascular adverse effects including congestive heart failure, severe hypotension, exacerbation of angina, ventricular asystole, sinus arrest, heart block | - Generally avoid concurrent use, particularly in patients predisposed to heart failure<br>- Closely monitor patient hemodynamic response and tolerance and adjust the dosage of one or both agents accordingly<br>- Advise patients to promptly report any symptoms including fatigue, headache, fainting, swelling of the extremities, weight gain, shortness of breath, chest pain, increased or decreased heartbeat, or irregular heartbeat |
| DDI-33 | procainamide + amiodarone | PD | Additive depressant effects on cardiac conduction | (Exacerbation of pre-existing) arrhythmias and QT prolongation | - Avoid concurrent use except for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or to amiodarone alone<br>- Reduce the dosage of both agents by one-third to one-half<br>- Monitor patients for conduction disturbances and exacerbation of tachyarrhythmia<br>- Advise patients to promptly report any symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light-headedness, fainting, palpitations, irregular heartbeat, shortness of breath, or syncope. |
| DDI-34 | procainamide + trimethoprim | PK | Increased procainamide exposure due to competition for active tubular excretion with trimethoprim | Cardiac adverse effects including QT prolongation, torsade de pointes, cardiac arrest | - Reduce the procainamide dosage. Monitor serum procainamide levels as well as patient response and adjust the procainamide dosage accordingly<br>- Patients should be advised to promptly report any signs of procainamide toxicity including drowsiness, dizziness, syncope, confusion, tremor or palpitations |
| DDI-35 | furosemide + etacrynic acid | PD | Additive or synergistic ototoxic effects | Ototoxicity with risk of tinnitus, reversible or irreversible hearing impairment, deafness | - Avoid concurrent use |
| DDI-36 | concomitant use of ≥ 3 centrally-acting drugs (i.e. opiates or antipsychotics or benzodiazepines/z-drugs or | PD | Additive depressant effect on central nervous system | Increased risk of falls and fracture, impaired cognition | - Minimise the number of CNS agents<br>- Limit the dosage and duration of each drug to the minimum possible while achieving the desired clinical effect<br>- Closely monitor patients for adverse effects |

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| | barbiturates or antiepileptics or antidepressants) | | | | |
| DDI-37 | alprazolam or diazepam or midazolam or triazolam or zolpidem or zopiclone + a CYP3A4 inhibitor (ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, diltiazem, verapamil, quinidine, dronedarone, amiodarone, ciclosporin, ritonavir, clarithromycin, erythromycin) | PK | Increased exposure to benzodiazepine and z-drugs due to the inhibition of CYP3A4-mediated metabolism | Excessive sedation and prolonged hypnotic effects | - Consider benzodiazepine/Z-drug dosage reduction<br>- Advise patients to promptly report any symptoms of nausea, vomiting, diarrhoea, confusion, daytime sedation, dizziness or unconsciousness |
| DDI-38 | SSRI + another serotonergic drug (including tramadol) | - PD<br>With tramadol: PD + PK | - Additive serotonergic actions<br>- With tramadol :<br>i) both drugs lower seizure threshold and<br>inhibition of CYP2D6-mediated conversion of tramadol into its active O-demethylated metabolite by SSRIs | - Serotonin syndrome<br>With tramadol: seizures and diminished therapeutic response to tramadol | - Closely monitor for symptoms of the serotonin syndrome such as hypertension, tachycardia, hyperthermia, myoclonus, mental status changes, particularly when initiating or increasing dosages of these agents. Consider potential risk even when administering serotonergic agents sequentially, as some of them may demonstrate prolonged elimination half-life (e.g. fluoxetine)<br>- With tramadol, use with caution regarding increased risk of seizure and monitor patient's therapeutic response<br>- When discontinuing a serotonergic CYP2D6 inhibitor in a patient receiving tramadol therapy, consider a tramadol dose reduction and monitor for signs of respiratory depression or sedation |
| DDI-39 | oral NSAID + SSRI or SNRIs | PD | NSAID potentiation of bleeding risk associated with antidepressants (additive effects on platelet inhibition, gastrointestinal irritation) | Bleeding, gastrointestinal bleeding | - Substitute with alternatives to NSAIDs (e.g. paracetamol) or less gastrotoxic NSAIDs (e.g. ibuprofen)<br>- Consider the addition of gastroprotective drugs (e.g. PPI, $H_2$ antagonists)<br>- Advise patients to promptly report any signs of excessive anticoagulation such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine colour, headache, dizziness or weakness |
| DDI-40 | fluoxetine + tricyclic antidepressant | PD + PK | - Additive serotonergic effects<br>- Additive effects on QT prolongation<br>- Increased exposure to tricyclic antidepressant due to the inhibition of CYP2D6- | - Serotonergic syndrome<br>Tricyclic antidepressant toxicity, including cardiac arrhythmias | - Consider tricyclic antidepressant dosage reduction and serum level monitoring, even several weeks after fluoxetine discontinuation<br>- Closely monitor patients for signs of tricyclic antidepressants toxicity (e.g. cardiac arrhythmias, sedation, dry mouth, blurred vision, constipation, urinary retention) and/or excessive serotonergic activity |

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| | | | mediated metabolism by fluoxetine | | (e.g. CNS irritability, altered consciousness, confusion, myoclonus, ataxia, abdominal cramping, hyperpyrexia, shivering, pupillary dilation, diaphoresis, hypertension, and tachycardia)<br>- If serotonin syndrome occurs, immediately discontinue fluoxetine and tricyclic antidepressants<br>- If ventricular arrhythmias develop, consider fluoxetine discontinuation and cardiac evaluation |
| DDI-41 | lithium + NSAID | PK | Decreased lithium renal excretion due to NSAID inhibition of renal prostaglandin synthesis and thus reduction of renal blood flow | Lithium toxicity, potentially life-threatening | - Extra caution is advised in a number of conditions including advanced age, impaired renal function, decreased sodium intake, volume depletion, renal artery stenosis, and heart failure as these increase the risk of toxicity.<br>- Reduce the lithium dosage, titrate slowly and frequently monitor serum concentrations<br>- Closely monitor patients for signs of lithium toxicity including drowsiness, dizziness, confusion, weakness, ataxia, tremor, tinnitus, blurred vision, nystagmus, vomiting, diarrhoea, thirst, diabetes insipidus (polyuria, polydipsia), seizure and ECG changes<br>- Advise patients to promptly report any signs of lithium toxicity (*listed above*) |
| DDI-42 | lithium + diuretic | PK | *Not fully understood*<br>Decreased lithium excretion due to compensatory distal reabsorption of sodium and lithium salt upon sodium loss induced by diuretics. | Lithium toxicity, potentially life-threatening | - Extra caution is advised in a number of conditions including advanced age, impaired renal function, decreased sodium intake, volume depletion, renal artery stenosis and heart failure<br>- Reduce the lithium dosage, titrate slowly, and frequently monitor serum concentrations<br>- Closely monitor patients for signs of lithium toxicity including drowsiness, dizziness, confusion, weakness, ataxia, tremor, tinnitus, blurred vision, nystagmus, vomiting, diarrhoea, thirst, diabetes insipidus (polyuria, polydipsia), seizure and ECG changes<br>- Advise patients to promptly report any signs of lithium toxicity (*listed above*) |
| DDI-43 | lithium + ACE inhibitor or an ARB | PK | *Not fully understood*<br>Decreased lithium excretion due to compensatory distal reabsorption of sodium and lithium salt upon sodium loss | Lithium toxicity, potentially life-threatening | - Extra-caution is advised in a number of conditions including advanced age, impaired renal function, decreased sodium intake, volume depletion, renal artery stenosis and heart failure<br>- Reduce the lithium dosage, titrate slowly, and frequently monitor serum concentrations |

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| | | | induced by ACE inhibitors and ARBs | | - Closely monitor patients for signs of lithium toxicity including drowsiness, dizziness, confusion, weakness, ataxia, tremor, tinnitus, blurred vision, nystagmus, vomiting, diarrhoea, thirst, diabetes insipidus (polyuria, polydipsia), seizure, ECG changes<br>- Advise patients to promptly report any signs of lithium toxicity (*listed above*) |
| DDI-44 | MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + sympathomimetic | PD | Excessive adrenergic response due to the inhibition of noradrenaline degradation by MAO inhibitors and potentiated by the action of sympathomimetics | Hypertensive crisis | - Concurrent use is contraindicated<br>- Wait at least 14 days after MAO inhibitor discontinuation before starting sympathomimetic use |
| DDI-45 | MAO-A inhibitor (i.e. moclobemide) or non-selective MAO inhibitor (i.e. phenelzine or linezolid) + levodopa | PD | Additive effects resulting in increased levels of dopamine and noradrenaline | Hypertensive crisis | - Avoid concurrent use even if carbidopa or benserazide are given in combination with levodopa<br>- Wait two to three weeks after MAO-A inhibitor discontinuation before starting levodopa treatment |
| DDI-46 | MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + some opioids (i.e. meperidine or fentanyl) | PD | *Not fully understood*<br>- Excessive serotonergic response<br>- Potentiation of CNS effect of opioids by MAO inhibitors | - Serotonin syndrome<br>Respiratory depression, cyanosis, hypotension and coma | - Concurrent use is contraindicated or not recommended<br>- Wait at least 14 days after MAO inhibitor discontinuation before starting an opioid |
| DDI-47 | MAO inhibitor (i.e. phenelzine, moclobemide, rasagiline, safinamide, selegiline, linezolid) + an antidepressant (particularly a SSRI) | PD | Additive serotonergic effects | Serotonin syndrome | - Concurrent use is contraindicated<br>- Wait at least 14 days between stopping a MAO inhibitor and starting another antidepressant; wait at least 7 to 14 days between stopping another antidepressant and starting a MAO inhibitor (5 weeks with fluoxetine)<br>- Monitor patients for signs of serotonin syndrome (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes) |
| DDI-48 | carbamazepine + verapamil or diltiazem | PK | - Increased carbamazepine exposure due to the inhibition of CYP3A4-mediated metabolism by verapamil and diltiazem<br>- Decreased exposure to verapamil and diltiazem due to the induction of CYP3A4-mediated metabolism by carbamazepine | - Carbamazepine toxicity<br>Decreased therapeutic effect of verapamil and diltiazem | - Closely monitor serum levels of carbamazepine when initiating or discontinuing verapamil or diltiazem<br>- Reduce carbamazepine dosage by one-half upon initiation of verapamil or diltiazem<br>- Advise patients to promptly report any signs of carbamazepine toxicity such as headache, nausea, vomiting, dizziness, confusion, slurred speech, nystagmus, visual disturbances, tremors and ataxia<br>- Monitor blood pressure and cardiac effect after initiating carbamazepine |

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| DDI-49 | carbamazepine + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | - Increased carbamazepine exposure due to the inhibition of CYP3A4-mediated metabolism (and P-gp) by some macrolides<br>- Decreased macrolide exposure due to the induction of CYP3A4-mediated metabolism by carbamazepine | - Carbamazepine toxicity<br>Decreased macrolide efficacy | - Closely monitor serum levels of carbamazepine and adjust the dosage accordingly<br>- Advise patients to promptly report any signs of carbamazepine toxicity such as headache, nausea, vomiting, dizziness, confusion, slurred speech, nystagmus, visual disturbances, tremors and ataxia<br>- Substitute with a non-macrolide antibiotic therapy or wait at least two weeks of discontinuing carbamazepine before using a macrolide. If co-administered, monitor patients for antimicrobial efficacy |
| DDI-50 | acetylcholinesterase inhibitor + a drug that reduces heart rate (i.e. antiarrhythmic drugs or beta-blockers or verapamil or diltiazem) | PD | Additive bradycardia | Bradycardia | - Use with caution, particularly in patients with increased risk of developing cardiac conduction disturbances<br>- Advise patients to promptly report any symptoms such as dizziness, light-headedness, fainting or irregular heartbeat |
| DDI-51 | theophylline + cimetidine | PK | Increased theophylline exposure due to CYP1A2-mediated metabolism by cimetidine | Theophylline toxicity | - Closely monitor the theophylline serum levels and adjust the dosage accordingly<br>- Advise patients to promptly report any signs of theophylline toxicity such as nausea, vomiting, diarrhoea, headache, seizures, restlessness, insomnia, or irregular heartbeat/palpitations |
| DDI-52 | theophylline + a quinolone | PK | Increased theophylline exposure due to the inhibition of CYP1A2-mediated metabolism | Theophylline toxicity | - Closely monitor theophylline serum levels and adjust the dosage accordingly<br>- Advise patients to promptly report any signs of theophylline toxicity such as nausea, vomiting, diarrhoea, headache, seizures, restlessness, insomnia, or irregular heartbeat/palpitations |
| DDI-53 | theophylline + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | Increased theophylline exposure due to the inhibition of CYP3A4-mediated metabolism by some macrolides | Theophylline toxicity | - Closely monitor theophylline serum levels and adjust the dosage accordingly<br>- Advise patients to promptly report any signs of theophylline toxicity such as nausea, vomiting, diarrhoea, headache, seizures, restlessness, insomnia, or irregular heartbeat/palpitations |
| DDI-54 | theophylline + fluvoxamine | PK | Increased theophylline exposure due to the inhibition of CYP1A2-mediated metabolism by fluvoxamine | Theophylline toxicity | - Substitute with other SSRI or reduce the theophylline dosage by one-third and closely monitor serum theophylline levels<br>- Advise patients to report any signs of theophylline toxicity such as nausea, vomiting, diarrhoea, anorexia, headache, tremor, irritability, confusion, insomnia, seizure, palpitations and arrhythmia |

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| DDI-55 | thiopurines (e.g. azathioprine) + allopurinol | PK | Increased exposure to the active metabolite of azathioprine (mercaptopurine) due to xanthine oxidase inhibition by allopurinol | Azathioprine toxicity | - Reduce the azathioprine dosage by one-quarter to one-third<br>- Closely monitor patients for hematologic toxicity (leukopenia, thrombocytopenia, anaemia)<br>- Advise patients to report any signs of thiopurine toxicity such as fever, chills, sore throat, fatigue, lethargy, pallor, anorexia, jaundice, dark urine, nausea, vomiting, signs of local infection and unusual bleeding or bruising |
| DDI-56 | oral or parenteral corticosteroid + an oral NSAID | PD | Additive gastrointestinal adverse effects | Gastrointestinal ulceration or bleeding | - Consider the addition of gastroprotective drugs (e.g. PPI, $H_2$ antagonists)<br>- Advise patients to report any signs of gastrointestinal ulceration and bleeding such as severe abdominal pain, dizziness, light-headedness and the appearance of black, tarry stools |
| DDI-57 | concomitant prescription of ≥ 2 anticholinergic drugs | PD | Additive anticholinergic effects | Anticholinergic effects including cognitive decline | - Minimise the number of anticholinergic drugs and consider non-anticholinergic alternatives<br>- Closely monitor patients for additive anticholinergic effects such as mydriasis, blurred vision, flushed face, fever, dry skin and mucous membranes, tachycardia, urinary retention, constipation, memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy and seizures<br>- Advise patients to promptly report any potential signs of anticholinergic effects such as abdominal pain, fever, heat intolerance, blurred vision, confusion or hallucinations |
| DDI-58 | ciclosporin + rifampicin | PK | Decreased exposure to immunosuppressants due to the induction of both CYP3A4-mediated metabolism and P-gp by rifampicin | Organ rejection | - Monitor serum levels of the immunosuppressant and adjust the dosage accordingly<br>- Monitor patient for signs of organ rejection |
| DDI-59 | ergot alkaloid (e.g. ergotamine) + some macrolides (i.e. erythromycin or clarithromycin or roxithromycin or telithromycin) | PK | Increased exposure to ergot derivatives due to the inhibition of CYP3A4-mediated metabolism by some macrolides | Ergot toxicity | - Concurrent use is contraindicated given the potential for ergot toxicity characterised by nausea, vomiting, peripheral vasospasm, ischemia, thrombosis, tachycardia and hypertension |
| DDI-60 | methotrexate + trimethoprim | PD + PK | *Not fully understood* | Potentially fatal methotrexate toxicity | - Closely monitor patients for hematologic toxicity (e.g. myelosuppression, pancytopenia, megaloblastic anaemic, severe bone marrow depression) |

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| | | | - Additive effects on dihydrofolate reductase inhibition<br>- Increased exposure to methotrexate due to protein binding displacement and reduced tubular excretion | | - Advise patients to promptly report any signs and symptoms of bone marrow depression or anaemia such as fever, chills, sore throat, easy bruising or bleeding, pallor, dizziness, fatigue, lethargy, sore mouth or tongue and tingling in hands or feet |
| DDI-61 | phosphodiesterase type 5-inhibitor + nitrate | PD | Additive effects on cGMP accumulation resulting in excessive blood vessels musculature relaxation | Severe hypotension, myocardial ischemia | - Concomitant use is contraindicated<br>- The time after when nitrates can be safely administered following PDE5 inhibitors use is uncertain and could go as far as 48 hours. Even then, closely monitor patients for hemodynamic response |
| DDI-62 | tamoxifen + vitamin K antagonist | Unknown | *Not understood* | Bleeding | - Concomitant use is contraindicated<br>- Consider using lower doses of vitamin K antagonist and closely monitor the INR |
| DDI-63 | tamoxifen + citalopram or escitalopram | PD | Additive effects on QT prolongation | Ventricular arrhythmias, torsade de pointes and sudden death | - Closely monitor patients for ECG changes<br>- Advise patients to promptly report any signs of toxicity such as drowsiness, dizziness, fainting/syncope, confusion or palpitations |
| DDI-64 | tamoxifen + paroxetine or fluoxetine or bupropion | PK | Decreased exposure to tamoxifen active metabolite due to the inhibition of CYP2D6-mediated metabolism by antidepressants | Reduced effectiveness of tamoxifen | - Consider other antidepressant with a limited impact in CYP2D6 activity or, eventually, aromatase inhibitors as tamoxifen substitutes |
| DDI-65 | concomitant prescription of ≥ 2 drugs that reduce potassium (e.g. β2-agonists, thiazides, loop diuretics, corticosteroids) | PD | Additive hypokalaemia | Hypokalaemia, QT prolongation and torsade de pointes | - Closely monitor serum potassium levels<br>- Advise patients to promptly report any signs of hypokalaemia such as fatigue, weakness, myalgia, muscle cramps, numbness, tingling, abdominal pain, constipation, palpitation, and irregular heartbeat. |
| DDI-66 | SSRI + loop or thiazide diuretic | PD | Additive hyponatraemia | Hyponatraemia, orthostatic hypotension | - Closely monitor patients' sodium levels, blood pressure and pulse<br>- Advise patient to avoid rising abruptly from a sitting or recumbent position and to promptly report any signs of hyponatraemia including nausea, vomiting, headache, confusion, lethargy, weakness |

ACE: angiotensin-converting enzyme; ARB: angiotensin II type 1 receptor blockers; CNS: central nervous system; CrCl: creatinine clearance; CYP: cytochrome P450; DDI: drug-drug interaction; ECG: electrocardiogram; H2: histamine-2-receptor; INR: International Normalised Ratio; MAO: Monoamine oxidase; NSAID: non-steroidal anti-inflammatory drug; OATP: organic anion transporting polypeptide; PD: pharmacodynamic; PDE5: phosphodiesterase type 5; PK: pharmacokinetic; P-gp: P-glycoprotein; PPI: proton pump inhibitor; SmPC: Summary of product characteristics; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

* For key principles to guide optimal use of the DDI list by clinicians, please refer to Table 3.

† Pharmacodynamic DDIs occur between drugs with additive or opposing effects. They can be anticipated based on knowledge of the clinical effects of the drugs involved (mode of action, organs affected in relation to action or side effects). Pharmacokinetic DDIs cannot be predicted from the clinical effects of the drugs involved. They require knowledge on the PK parameters (absorption, distribution, metabolism and elimination) of each drug, and these parameters may vary between drugs of the same pharmacological class.

**Appendix 6**: Summary of the DDI list, per medication class (A), and per type of adverse event and medication class (B)

| **A. Drugs most frequently involved in DDIs** |
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| **Cardiovascular** |
| Digoxin |
| Anti-arrythmics |
| Calcium channel blockers |
| ACE inhibitors / ARBs |
| Lipid-modifying agents |
| Diuretics |
| **Coagulation** |
| VKA |
| DOAC |
| Antiplatelet agents |
| **Infections** |
| Macrolides |
| Trimethoprim + sulfamethoxazole |
| Quinolones |
| **Central nervous system** |
| Combination: ≥3 centrally-active drugs |
| MAO-inhibitor |
| SSRI / SNRI |
| Tricyclic antidepressants |
| Lithium |
| **Musculo-skeletal system** |
| NSAID |
| **Respiratory system** |
| Theophylline |

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin II type 1 receptor blockers; CNS: Central Nervous System ; DOAC: Direct oral anticoagulant ; MAO: Monoamine oxydase; NSAID: non-steroidal anti-inflammatory drug; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VKA: Vitamin K Antagonists

B. Drug-drug interactions classified by type of adverse event and by medication class

| | Cardiovascular | Coagulation | Infections | CNS | Other |
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| **Bleeding** | | | | | |
| | amiodarone (10)<br>fibrate (7) | VKA (7-15;62)<br>DOAC (16-19)<br>DOAC-VKA (11;12)<br>Antiplatelet (12;20) | metronidazole (9)<br>trimethoprim-sulfamet(13)<br>macrolide (15)<br>quinolone (14) | SSRI; SNRI (39) | PgP/CYP3A4 inhibitors (16-19)<br>cimetidine (8)<br>NSAID (11;20;39;56)<br>Corticosteroid (56)<br>tamoxifen (62) |
| **Cardiovascular effects** | | | | | |
| Congestive heart failure | Diuretic (24)<br>beta-blocker (32)<br>verapamil, diltiazem(32) | | | | NSAID (24) |
| Heart block | disopyramide (31)<br>beta-blocker (32)<br>verapamil, diltiazem (32) | | macrolide (31) | | |
| QT prolongation, torsade de pointe | disopyramide (31)<br>procainamide (33; 34)<br>amiodarone (34) | | macrolide (31)<br>trimethoprim (34) | (es)citalopram (63) | Drugs that reduce potassium (65)<br>tamoxifen (63) |
| Bradycardia | Calcium channel blocker (30)<br>antiarrythmic (50)<br>beta-blocker (32; 50)<br>verapamil, diltiazem (32; 50) | | | acetylcholinesterase inhibitor (50) | PgP/CYP3A4 inhibitors (30) |
| Digoxin toxicity (potential fatal cardiac arrhythmia) | digoxin (1;2;3;4;5;6)<br>quinidine (4)<br>amiodarone (1)<br>verapamil, diltiazem (2)<br>thiazide, loop diuretics (6)<br>propafenone (3) | | macrolide (5) | | |
| **Blood pressure control** | | | | | |
| Hypertension | ACEI, ARB (23)<br>Diuretic (25) | | | MAO-inhibitor (44;45)<br>levodopa (45) | NSAID (23-24)<br>sympathomimetic (44) |
| Hypotension | Nitrate (61) | | | | phosphodiesterase type 5 inhibitor (61) |
| **Electrolytes disturbances** | | | | | |
| Hyperkalemia | Diuretic (21;22;24)<br>ACEI, ARBs (21-23) | | trimethoprim-sulfamet (21) | | NSAID (21;23;24)<br>Potassium supplement (22) |
| Hypokalemia | | | | | ≥2 drugs that reduce potassium (65) |
| Hyponatremia | loop, thiazide diuretic (66) | | | SSRI (66) | |
| Deterioration of renal function | ACEI, ARB (23)<br>Diuretic (24) | | | | NSAID (23;24) |
| **CNS toxicity** | | | | | |
| Impaired cognition, falls and fracture, excessive sedation | | | | Benzodiazepine/Z-drug (36;37)<br>≥3 centrally-active drugs (37) | CYP3A4 inhibitors (37) |
| Anticholinergic effects, including cognitive decline | | | | | ≥2 anticholinergic drugs (57) |
| Serotonin syndrome | | | | SSRI (38; 40; 47)<br>tricyclic antidepressant (40)<br>tramadol (38)<br>Opioid (46)<br>MAO inhibitor (46)<br>antidepressant (47) | serotoninergic drug (48) |
| **Specific drug toxicity** | | | | | |
| Lithium toxicity | Diuretic (42)<br>ACEI, ARB (43) | | | Lithium (41-43) | NSAID (41) |
| Carbamazepine toxicity | verapamil, diltiazem (48) | | macrolide (49) | carbamazepine (48;49) | |
| Theophylline toxicity | | | macrolide (53)<br>quinolone (52) | fluvoxamine (54) | theophylline (51-54)<br>cimetidine (51) |
| Azathioprine toxicity | | | | | Thiopurine (55)<br>allopurinol (55) |
| Ergot toxicity | | | macrolide (59) | ergot alkaloid (59) | |
| Methotrexate toxicity | | | trimethoprim (60) | | methotrexate (60) |
| **Others** | | | | | |
| Anticholinergic effects | | | | | ≥2 anticholinergic drugs (60) |
| Myopathy/ rhabdomyolysis | Statin (25-29)<br>gemfibrozil (25)<br>diltiazem, verapamil (26)<br>amlodipine (27)<br>amiodarone (28) | | macrolide (29) | | |
| Organ rejection | | | rifampicin (58) | | cyclosporine (58) |
| Ototoxicity | furosemide (35)<br>etacrinic acid (35) | | | | |
| Tamoxifen reduced effectiveness | | | | paroxetine, fluoxetine, bupropion (64) | tamoxifen (64) |

Legend: Blue cells refer to pharmacodynamic drug interactions; orange cells refer to pharmacokinetic interactions (light orange: drug affecting; dark orange: drug affected); orange cells with blue text refer to drugs interactions that are both pharmacokinetic and pharmacodynamic by nature;

uncoloured cells refer to DDIs for which the mechanism is not fully understood. Numbers in bracket refer to the number of the drug interaction (see Table 3).

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin II type 1 receptor blockers; CNS: Central Nervous System ; DOAC: Direct oral anticoagulant; GI: Gastro-Intestinal; MAO: Monoamine oxidase; NSAID: non-steroidal anti-inflammatory drug; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VKA: Vitamin K Antagonist