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ORIGINAL REPORT

The burden and management of cytochrome P450 2D6 (CYP2D6)-mediated drug–drug interaction (DDI): co-medication of metoprolol and paroxetine or fluoxetine in the elderly

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ABSTRACT

Purpose Metoprolol and paroxetine/fluoxetine are inevitably co-prescribed because cardiovascular disorders and depression often coexist in the elderly. This leads to CYP2D6-mediated drug–drug interactions (DDI). Because systematic evaluations are lacking, we assessed the burden of metoprolol–paroxetine/fluoxetine interaction in the elderly and how these interactions are managed in Dutch community pharmacies.

Method Dispensing data were collected from the University of Groningen pharmacy database (IADB.nl, 1999–2014) for elderly patients (≥60 years) starting beta-blockers and/or antidepressants. Based on the two main DDI alert systems (G-Standard and Pharmabase), incidences were divided between signalled (metoprolol–fluoxetine/paroxetine) and not-signalled (metoprolol-alternative antidepressants and alternative beta-blockers–paroxetine/fluoxetine) combinations. Incident users were defined as patients starting at least one signalled or a non-signalled combination. G-Standard signalled throughout the study period, whereas Pharmabase stopped after 2005.

Results A total of 1763 patients had 2039 metoprolol–paroxetine/fluoxetine co-prescriptions, despite DDI alert systems, and about 57.3% were signalled. The number of metoprolol-alternative antidepressant combinations (incidences = 3150) was higher than alternative beta-blocker–paroxetine/fluoxetine combinations (incidences = 1872). Metoprolol users are more likely to be co-medicated with an alternative antidepressant (incidences = 2320) than paroxetine/fluoxetine users (incidences = 1232) are. The number of paroxetine/fluoxetine users co-prescribed with alternative beta-blockers was comparable to those co-medicated with metoprolol (about 50%). Less than 5% of patients received a substitute therapy after using metoprolol–paroxetine/fluoxetine. Most of the metoprolol users (90%) received a low dose (mean DDD = 0.47) regardless whether they were prescribed paroxetine/fluoxetine.

Conclusion Despite the signalling software, metoprolol–paroxetine/fluoxetine combinations are still observed in the elderly population. The clinical impact of these interactions needs further investigation. Copyright © 2017 John Wiley & Sons, Ltd.

KEY WORDS—cytochrome P450 (CYP)-based drug–drug interactions (DDI); CYP2D6; paroxetine/fluoxetine; metoprolol; beta-blockers; antidepressants; pharmacoepidemiology

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INTRODUCTION

Cytochrome P450 (CYP)-based drug–drug interactions (DDIs) are common in clinical practice and often involve older patients with polypharmacy.[1,2]

Several studies reported that DDI might increase hospitalization rates.[3] CYP enzyme-related DDIs are quite prevalent in chronic diseases such as cardiovascular diseases and psychiatric illnesses which frequently coexist in the elderly.[4–7]

Beta-blockers are a class of drugs widely prescribed to treat cardiovascular diseases, and potentially related to DDI.[8,9] The beta-1 selective metoprolol is one of the most efficacious beta-blockers.[10,11] An important

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limitation is, however, that metoprolol can induce bradycardia.[12,13] Metoprolol is extensively metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme, which is associated with an interindividual variation including the absence of activity due to genetic polymorphism.[14] Patients with a CYP2D6 genotype related to inactivity of this enzyme, or those using a drug which inhibits it, can develop metoprolol-related adverse effects.[15,16]

Individuals with cardiovascular diseases frequently suffer from a depressive illness and vice versa.[17–19] Selective serotonin reuptake inhibitors (SSRIs) are currently a preferred medication for treating these depressed patients.[20] SSRIs and metoprolol are thus often co-prescribed.[15,21,22] The commonly prescribed SSRIs, paroxetine and fluoxetine, have a strong affinity for CYP2D6 and may convert the phenotype of patients who are normally extensive CYP2D6 metabolizers (EM) become poor metabolizers (PM).[23,24]

Several publications have reported that paroxetine and fluoxetine significantly alter the pharmacokinetics of metoprolol, leading to toxicities.[13,15,25,26] However, some population studies indicate that DDIs have no clinical significance.[21,22]

To prevent CYP-based DDI, medication in the Netherlands is dispensed in pharmacies after electronic screening by a DDI alert system.[27,28] Currently, there are two main DDI alert systems: G-Standard from the 'Royal Dutch Association for the Advancement of Pharmacy' (KNMP) (about 45% of the pharmacies) and Pharmabase from the Health Base Foundation (about 55% of pharmacies). Before 2005, both pharmacy systems signalled the metoprolol–paroxetine/fluoxetine. However, only the KNMP database has continued to signal this DDI since 2005, due to a different interpretation of its clinical relevance.

The role of DDI alerts in minimizing DDI has been documented.[29] However, the DDI alert system has some drawbacks, such as the 'alert fatigue phenomenon' which leads to failure to act on alerts.[30,31] Indeed, there is ample evidence that prescribers, and community pharmacists, are commonly not compliant with the recommendations provided by the alert system.[28,31–34] Buurma *et al.* reported that the national guidelines for resolving DDI are not applied appropriately in Dutch pharmacies.[28] However, this study did not consider the type of the DDI alerts used in the Dutch community pharmacies and the differences in the DDI alerts. This study, therefore, aimed to assess the burden of metoprolol and paroxetine/fluoxetine interactions in the elderly population, and how the interaction was handled, based on the information provided by DDI alert systems in Dutch community pharmacies.

METHOD

Setting

This study was performed using the University of Groningen community pharmacy prescription database IADB.nl. It contains prescription records from 1994 to 2014 for about 600 000 individuals. The information provided are date of birth, gender, longitudinal prescription data, Anatomical Therapeutic Chemical codes, dispensing date, amount prescribed, daily doses, estimated duration of drug consumption and prescriber code. Patient and prescription data can be compiled using a patient-specific identifier. The IADB is updated annually, and the population is considered representative of the Dutch population.[35] It has been used in many drug studies as a reliable data source.[36–38]

Guideline on metoprolol and paroxetine/fluoxetine co-administration

The G-Standard (KNMP) recommendations for the metoprolol–fluoxetine/paroxetine combination are to replace metoprolol with alternative beta-blockers or to replace fluoxetine/paroxetine with alternative antidepressants. If the combination is prescribed, nonetheless, practitioners are asked to consider lowering the metoprolol dose or informing the patient about potential side effects (//kennisbank.knmp.nl/).

The Pharmabase (Health Base Foundation) recommendation was identical to KNMP until mid-2005, after which it was discontinued.

Study population, exposure and outcome definition

The study population was selected from the IADB.nl based on the first prescription of beta-blockers (C07A) and/or antidepressants (N06A) for elderly patients (≥60 years old) from 1 January 1999 to 31 December 2014 and present in the database for at least 180 days before the first prescription. 'First prescription' for these drugs was defined as their not having been prescribed for 180 days or more before the 'first prescription' date.

Exposures were beta-blockers and antidepressants combinations. Beta-blockers and antidepressants combinations were recorded as the period during which the beta-blockers were dispensed along with antidepressants and vice versa. There were two

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possibilities: (i) the beta-blockers and antidepressants were co-prescribed from the same start date or (ii) the beta-blockers and antidepressants were not prescribed on the same day but coincided for a period.

These co-prescriptions were then divided based on the alert system applied in Dutch community pharmacies: G-Standard and Pharmabase. The signalled combination was metoprolol–fluoxetine/paroxetine: this combination was signalled from 1995 until mid-2005 by Pharmabase, and during the whole study period (1999–2014) by G-Standard. The non-signalled combinations were metoprolol-alternative antidepressants and alternative beta-blockers–paroxetine/fluoxetine co-medication.

The alternative antidepressant agents included in this study are SSRIs (citalopram, sertraline, escitalopram and fluvoxamine) and Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) (venlafaxine) as non-potent CYP2D6 inhibitors.[39] The alternative beta-blockers included in this study are based on the KNMP recommendation (bisoprolol, carvedilol and nebivolol), and also based on other prescriptions observed in the IADB.nl (atenolol, sotalol and propranolol) as non-potent CYP2D6 substrates.

The outcomes were categorized as cumulative incidences and incident users. Incidences were counted on the basis of the signalled and non-signalled combinations as well as changes in therapy. Incident users were defined as patients experiencing any of the outcomes. Therefore, a single patient could have several incidences.

The adjustments of signalled combinations according to the KNMP guideline were defined as follows:

- 'Replace metoprolol':
  1. Alternative beta-blockers were combined with paroxetine/fluoxetine, where the co-medication began simultaneously, or where alternative beta-blockers were co-dispensed during paroxetine/fluoxetine use.
  2. Metoprolol and paroxetine/fluoxetine were co-dispensed, and metoprolol was switched to another beta-blocker less than 84 days after the metoprolol was started. A switch within 84 days was assumed to be based on the guideline because the efficacy of beta-blockers is assessed after 12 weeks.[40]
- 'Replace fluoxetine/paroxetine':
  1. Alternative antidepressants were co-dispensed with metoprolol where the combination began simultaneously, or where alternative antidepressants were co-prescribed during metoprolol use.
  2. Metoprolol and paroxetine/fluoxetine were co-dispensed, and paroxetine/fluoxetine was switched to another antidepressant less than 45 days after the start of paroxetine/fluoxetine. A switch within 45 days was assumed to be based on the guideline since the efficacy of an antidepressant is assessed after six weeks of therapy.[41]
- 'Reduced metoprolol dose' was defined as a mean daily dose (expressed as Defined Daily Dose/DDD) of metoprolol less than 1 DDD and lower than the reference group when it was co-dispensed with paroxetine/fluoxetine. The reference group was defined as metoprolol users without paroxetine/fluoxetine.

RESULTS

Characteristics of incident users of beta-blockers and antidepressants

As shown in Table 1, there were 1763 users for 2039 incidences of signalled combination in the IADB.nl during the study period. More than half were signalled by the DDI alerting system when they were combined (39% by the G-Standard and 18.3% by Pharmabase before 2005). Metoprolol–paroxetine was a more common (around 85%) signalled co-medication than metoprolol–fluoxetine. Alternative antidepressant–metoprolol was the most prevalent non-signalled co-prescription (incident users = 2836; incidences = 3150), with citalopram being the most prescribed alternative antidepressant (>50%), venlafaxine the second (24%) followed by fluvoxamine, sertraline and escitalopram (<10%). In addition, there were comparable numbers of incident users (1655) and incidences (1872) of paroxetine/fluoxetine–alternative beta-blocker co-medications, more than 80% of which were a paroxetine combination. The top four alternative beta-blockers were atenolol (about 35%), bisoprolol (around 25%), sotalol (16 to 18%) and propranolol (about 16%). Nebivolol and carvedilol were less common, each of them accounting for less than 5%.

Most incident users of metoprolol–paroxetine/fluoxetine were women (>60%). Comparable female proportions were also found for alternative antidepressants–metoprolol and alternative beta-blockers–paroxetine/fluoxetine users, except for nebivolol–fluoxetine and carvedilol–paroxetine/fluoxetine users (Figure 1).

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Table 1. Incidences and incident users of beta-blocker and antidepressant combinations

Antidepressants	Metoprolol			
	Incident users[#]		Incidences*	
	n	%	*n*	%
Signalled combination				
Paroxetine	1484	84.2	1729	84.8
Fluoxetine	279	15.8	310	15.2
Total metoprolol—paroxetine/fluoxetine	1763	100	2039	100
Non-signalled combination				
Alternative antidepressants				
Citalopram	1523	53.7	1691	53.7
Venlafaxine	683	24.1	761	24.2
Fluvoxamine	235	8.3	256	8.1
Sertraline	218	7.7	249	7.9
Escitalopram	177	6.2	193	6.1
Total metoprolol—alternative antidepressant	2836	100	3150	100
Alternative beta-blockers	Paroxetine			
	Incident users		Incidences	
	n	%	*n*	%
Atenolol	471	28.4	536	28.6
Bisoprolol	335	20.2	367	19.6
Sotalol	246	14.9	274	14.6
Propranolol	226	13.7	250	13.3
Nebivolol	55	3.3	62	3.3
Carvedilol	26	1.6	29	1.5
Total	1359	82.1	1518	81.1
Alternative beta-blockers	Fluoxetine			
	Incident users		Incidences	
	n	%	*n*	%
Atenolol	103	6.2	119	6.4
Bisoprolol	74	4.5	85	4.5
Sotalol	48	2.9	57	3.0
Propranolol	48	2.9	62	3.3
Nebivolol	10	0.6	15	0.8
Carvedilol	13	0.8	16	0.8
Total	296	17.9	354	18.9
Total alternative beta-blockers—paroxetine/fluoxetine	1655	100	1872	100

*Incidences defined as overlapping prescription of antidepressants and beta-blockers.
[#]Incident users defined as patients experiencing incidences.

People aged 60 to 75 years (>50%) were more likely to have incidences of signalled and non-signalled combinations than older individuals, except citalopram–metoprolol and nebivolol–fluoxetine users (Figure 1).

Trends for beta-blockers–antidepressants combination

The trend for metoprolol–paroxetine co-administration fluctuated during the observation period (Figure 2). Peaking in 2001, it dropped from 2002 onwards, with a temporary increase after 2005. In contrast, the use of the metoprolol–citalopram combination increased steadily and then dropped sharply in 2005. It then became the most frequently co-prescribed drug from 2008 on. Venlafaxine–metoprolol, as the third most common combination, was co-prescribed more frequently than fluoxetine–metoprolol in most years. The other drug combinations showed a comparable trend to each other.

When combined with paroxetine/fluoxetine, metoprolol was the most common beta-blocker (Figure 2). Atenolol was the second-most co-prescribed beta-blocker, with a downward trend in the last observation period. Conversely, bisoprolol co-prescriptions were comparable to sotalol and propranolol at first but became more common in the last observation period. Use of propranolol and sotalol fluctuated, while nebivolol and carvedilol showed trends comparable to the least commonly co-dispensed drugs.

Application of 'replace paroxetine/fluoxetine'

Metoprolol was prescribed with paroxetine or fluoxetine for 60% of metoprolol–paroxetine/fluoxetine combinations (Table 2). Most of them were signalled by the DDI alert system when they were co-prescribed (38% by the G-Standard and 21% by Pharmabase before 2005). In contrast, a larger number of metoprolol prescriptions (>70%) were co-prescribed with alternative antidepressants (non-signalled combination). G-Standard and Pharmabase (before 2005) screened about 43% and 12% of these combinations, respectively.

The effect of the change in the Pharmabase DDI alert system might be indicated by the increase in metoprolol co-dispensed with paroxetine/fluoxetine, which had previously been screened by Pharmabase, from 21% before 2005 to 40% after 2005. This trend was not observed in the G-Standard (20% before 2005 and 19% after), because the relevant co-medication screening did not change.

Another way to interpret 'replace CYP2D6 inhibitor' is to replace paroxetine/fluoxetine with another antidepressant. Paroxetine and fluoxetine were replaced in 1% and 3% of prescriptions, respectively, and more than half were screened by Pharmabase from 2005 (not being signalled). Citalopram and venlafaxine were the most common drugs used to replace paroxetine/fluoxetine (Table 3).

Implementation of 'replace metoprolol'

About half the paroxetine/fluoxetine–metoprolol combinations were paroxetine/fluoxetine co-dispensed with metoprolol. More than half were signalled

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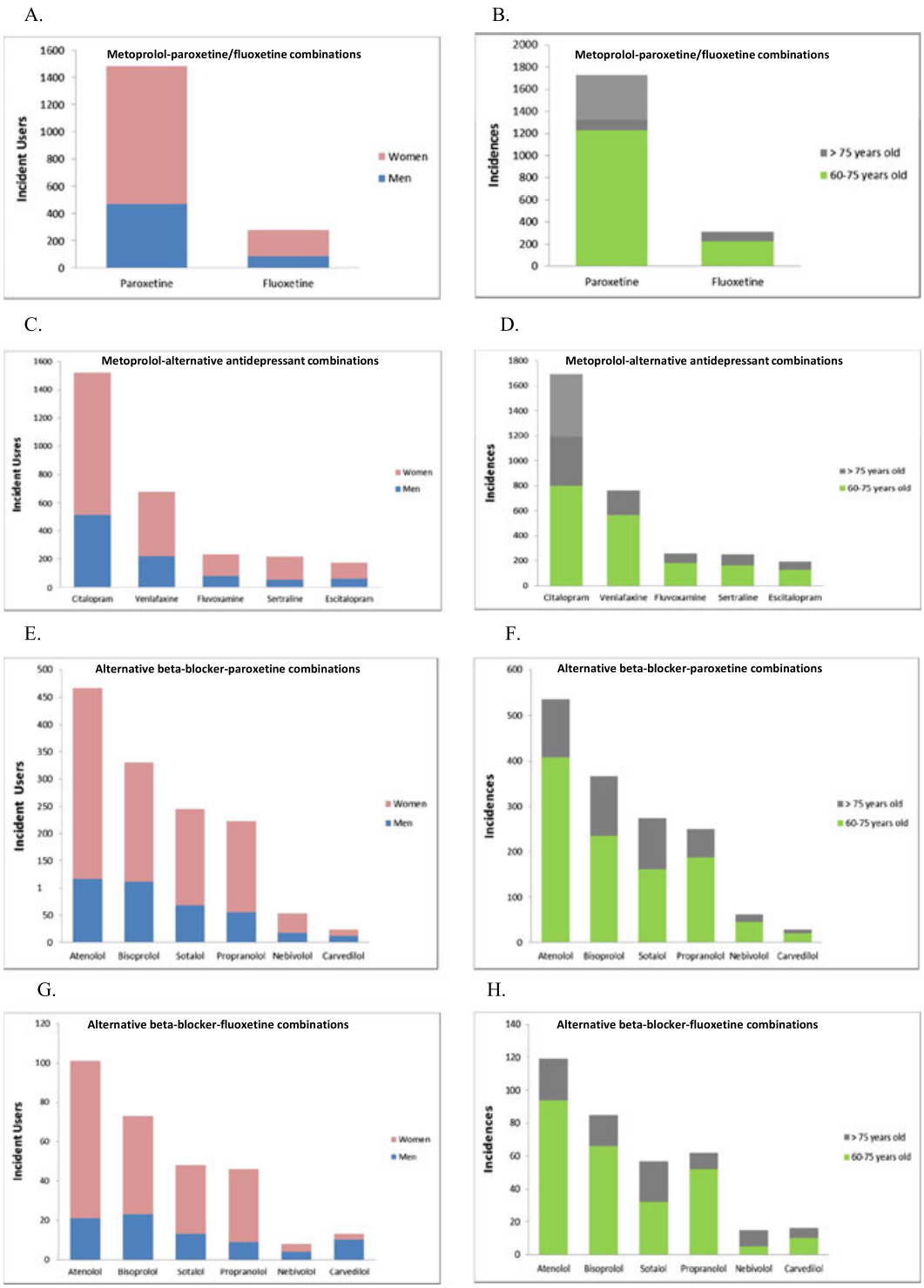

Figure 1. Gender and age distribution at the start of the combination. (A and B) Metoprolol and paroxetine/fluoxetine combination; (C and D) metoprolol and alternative antidepressant combination; (E and F) alternative beta-blockers and paroxetine combination; (G and H) alternative beta-blocker and fluoxetine combination. Incidences defined as overlapping prescription of antidepressants and beta-blockers. Incident users defined as patients experiencing incidences. [Colour figure can be viewed at wileyonlinelibrary.com]

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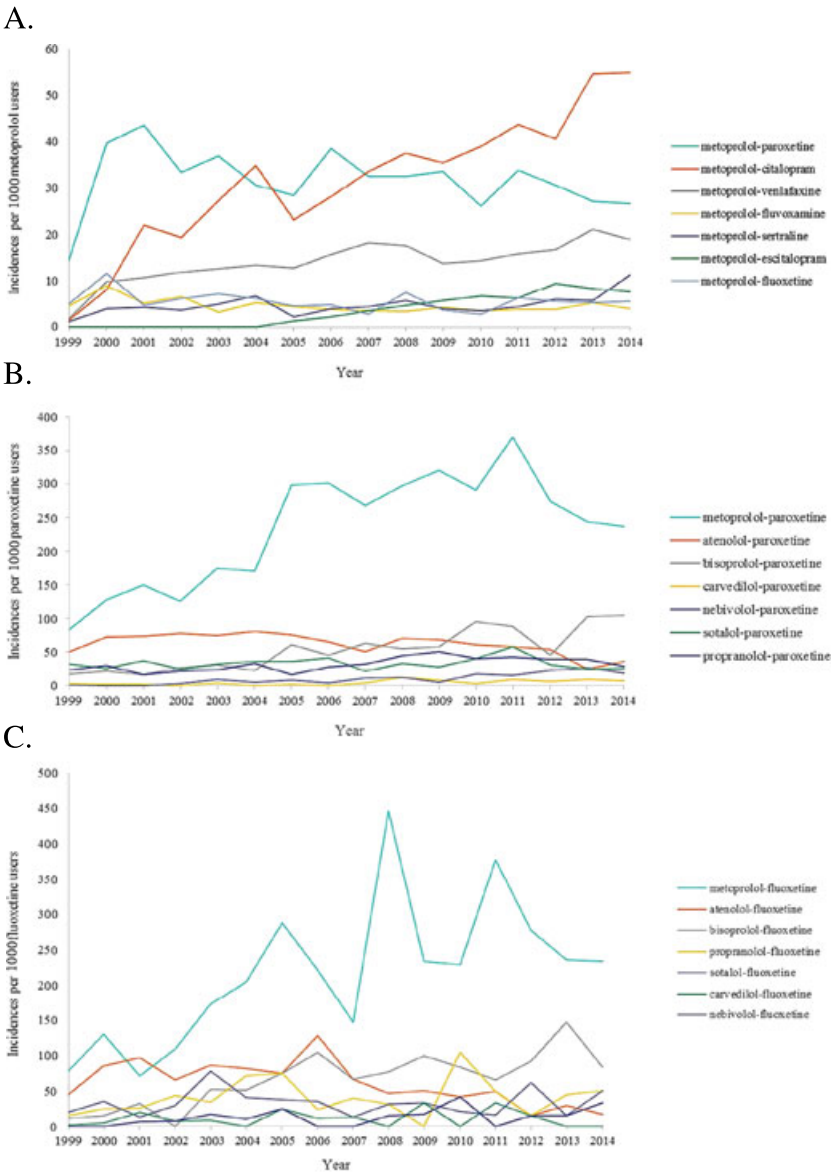

Figure 2. Co-medication trend per year in the period 1999 to 2014 in elderly patients in the IADB (≥60 years old). (A) Metoprolol-antidepressant incidences per 1000 metoprolol users; (B) beta-blockers–paroxetine incidences per 1000 paroxetine users; (C) beta-blockers-fluoxetine incidences per 1000 fluoxetine users. Incidences defined as overlapping prescription of antidepressants and beta-blockers. Users defined as patients prescribed with metoprolol (A), paroxetine (B) or fluoxetine (C). [Colour figure can be viewed at wileyonlinelibrary.com]

(paroxetine: around 41 and 13% by G-Standard and Pharmabase (before 2005), respectively; fluoxetine: around 36 and 20% by G-Standard and Pharmabase (before 2005), respectively). Alternative beta-blockers were co-administrated with paroxetine/fluoxetine prescriptions in equal proportions (around 50%) (Table 4).

The Pharmabase decision to stop signalling this DDI may also explain the considerable increase in paroxetine (from 13 to 46%) and fluoxetine (from 20 to 43%) prescriptions combined with metoprolol screened by Pharmabase from 2005. In contrast, paroxetine (from 14 to 27%) and fluoxetine co-prescriptions (from 14 to 22%) with metoprolol screened by G-Standard from 2005 only rose slightly.

Furthermore, metoprolol was substituted with another beta-blocker after co-administration with paroxetine/fluoxetine in fewer than 1.5% of cases. Paroxetine–metoprolol was more likely to be changed than fluoxetine–metoprolol. About 60 and 100% of the respective switch incidences for paroxetine–metoprolol and fluoxetine–metoprolol combinations had previously been signalled by the DDI alert

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Table 2. Proportion of metoprolol–antidepressant combinations

Combination of metoprolol	Number	Metoprolol first		Same start date		Total 'metoprolol co-prescribed with antidepressants'		DDI alerting system							
								Pharmabase				G-Standard			
								Before 2005		2005 and after		Before 2005		2005 and after	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Signalled combination															
Paroxetine															
Incidences	1729	924	53.4	118	6.8	1042	60.2	212	20.3	447	42.9	189	18.1	194	18.6
Incident users	1484	821	55.3	118	8	939	63.3	194	20.6	394	42	179	19.1	172	18.3
Fluoxetine															
Incidences	310	157	50.7	33	10.6	190	61.3	48	25.3	61	32.1	42	22.1	39	20.5
Incident users	279	141	50.5	33	11.8	174	62.3	39	22.4	56	32.2	41	23.6	38	21.8
Total incidences*	2039	1081	53	151	7.4	1232	60.4	260	21.1	508	41.2	231	18.8	233	18.9
Total incident users#	1763	962	54.6	151	8.5	1113	63.1	233	21	450	40.4	220	19.8	210	18.9
Non-signalled combination															
Citalopram															
Incidences	1691	1254	74.2	99	5.8	1353	80	130	9.6	634	46.9	135	9.9	454	33.6
Incident users	1523	1161	76.2	97	6.4	1258	82.6	125	9.9	591	47	130	10.3	412	32.8
Venlafaxine															
Incidences	761	438	57.6	51	6.7	489	64.3	55	11.2	219	44.8	67	13.7	148	30.3
Incident users	683	410	60	49	7.2	459	67.2	51	11.1	208	45.3	65	14.2	135	29.4
Fluvoxamine															
Incidences	256	116	45.3	28	10.9	144	56.2	49	34	52	36.1	26	18.1	17	11.8
Incident users	235	113	48.1	28	11.9	141	60	48	34	50	35.5	26	18.4	17	12.1
Sertraline															
Incidences	249	167	67.1	12	4.8	179	71.9	33	18.4	76	42.5	22	12.3	48	26.8
Incident users	218	147	67.4	12	5.5	159	72.9	32	20.1	65	40.9	20	12.6	42	26.4
Escitalopram															
Incidences	193	147	76.2	8	4.1	155	80.3	0	0	77	49.7	0	0	78	50.3
Incident users	177	138	78	8	4.5	146	82.5	0	0	73	50	0	0	73	50
Total incidences*	3150	2122	67.4	198	6.3	2320	73.7	267	11.5	1058	45.6	250	10.8	745	32.1
Total incident users#	2836	1969	69.4	194	6.8	2163	76.2	256	11.8	987	45.6	241	11.1	679	31.4

DDI, drug–drug interaction.
*Incidences defined as overlapping prescription of beta-blockers and antidepressants.
#Incident users defined as patients experiencing incidences.

systems. Bisoprolol and sotalol were the most common substitutes for metoprolol when combined with paroxetine. Sotalol and propranolol were the common substitutes for metoprolol when combined with fluoxetine (Table 3).

Dose reduction in metoprolol–paroxetine/fluoxetine combination

Most (90%) metoprolol users received a low dose (mean DDD 0.47), on its own or with paroxetine/fluoxetine. 1 DDD of metoprolol was never prescribed with paroxetine/fluoxetine, and only 0.1% of metoprolol-only users received 1 DDD. Slightly more patients received >1 DDD of metoprolol on its own (11%) than with paroxetine/fluoxetine (9% and 10%) (Table 5).

Although lowering paroxetine/fluoxetine dose is not in the guideline, we checked the paroxetine/fluoxetine dose because the degree of CYP2D6 inhibition is dose dependent.[42,43] Paroxetine/fluoxetine–metoprolol co-medications usually received 1 DDD paroxetine (41%) or fluoxetine (53%). Comparable percentages were also indicated when paroxetine (49%) and fluoxetine (57%) were prescribed without metoprolol. Similarly, the proportions accounted for low-dose paroxetine and fluoxetine (mean DDD 0.7 and 0.8, respectively) dispensed with and without metoprolol were comparable (paroxetine combination = 37%, paroxetine alone = 30%; fluoxetine combination = 19%, fluoxetine alone = 18%). Some (>20%) received >1 DDD of paroxetine/fluoxetine regardless of the metoprolol prescription.

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Table 3. Proportion of switching after paroxetine/fluoxetine–metoprolol co-administration

	Paroxetine–metoprolol				DDI alert system								Fluoxetine–metoprolol				DDI alert system							
					Pharmabase				G-Standard								Pharmabase				G-Standard			
	Incidences* (n = 1729)		Incident users# (n = 1484)		Before 2005		2005 and after		Before 2005		2005 and after		Incidences* (n = 310)		Incident users# (n = 279)		Before 2005		2005 and after		Before 2005		2005 and after	
Switch drugs	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Alternative antidepressants																								
Citalopram	11	0.6	11	0.7	1	9.1	7	63.6	1	9.1	2	18.2	4	1.3	4	1.4	0	0	2	50	1	25	1	25
Venlafaxine	9	0.5	9	0.6	2	22.2	5	55.5	0	0	2	22.2	3	1	3	1.1	1	33.3	2	66.7	0	0	0	0
Fluvoxamine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sertraline	0	0	0	0	0	0	0	0	0	0	0	0	2	0.6	2	0.7	0	0	1	50	0	0	1	50
Escitalopram	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	20	1.2	20	1.3	3	15	12	60	1	5	4	20	9	2.9	9	3.2	1	11.1	5	55.6	1	11.1	2	22.2
Alternative beta-blockers																								
Atenolol	2	0.1	2	0.1	0	0	2	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bisoprolol	6	0.3	6	0.4	0	0	3	50	0	0	3	50	0	0	0	0	0	0	0	0	0	0	0	0
Sotalol	6	0.3	6	0.4	2	33.3	1	16.7	1	16.7	2	33.3	1	0.3	1	0.4	1	100	0	0	0	0	0	0
Propranolol	3	0.2	3	0.2	2	66.7	0	0	0	0	1	33.3	1	0.3	1	0.4	1	100	0	0	0	0	0	0
Nebivolol	2	0.1	2	0.1	0	0	2	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carvedilol	1	0.1	1	0.1	0	0	0	0	0	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0
Total	20	1.1	20	1.3	4	20	8	40	1	5	7	35	2	0.6	2	0.8	2	100	0	0	0	0	0	0

DDI, drug–drug interaction.
*Incidences defined as overlapping prescription of antidepressants and beta-blockers.
#Incident users defined as patients experiencing incidences.

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Table 4. Proportion of beta-blocker–paroxetine/fluoxetine co-prescriptions

		Combination of paroxetine													
								DDI alert system							
		Paroxetine first		Same start date		Total paroxetine co-dispensed with beta-blockers		Pharmabase				G-Standard			
Drugs	*N*	*n*	%	*n*	%	*n*	%	Before 2005		2005 and after		Before 2005		2005 and after	
								n	%	*n*	%	*n*	%	*n*	%
Signalled combination															
Metoprolol															
Incidences*	1729	687	39.7	118	6.8	805	46.5	109	13.5	367	45.6	110	13.7	219	27.2
Incident Users[#]	1484	545	36.7	118	8	663	44.7	99	14.9	299	45.1	89	13.4	176	26.5
Non-signalled combination															
Alternative beta-blockers															
Atenolol															
Incidences	536	174	32.5	57	10.5	231	43	80	34.6	54	23.4	49	21.2	48	20.8
Incident users	471	169	35.9	56	11.9	225	48	79	35.1	52	23.1	48	21.3	46	20.4
Bisoprolol															
Incidences	367	186	50.7	22	6	208	56.7	23	11.1	77	37	19	9.1	89	42.8
Incident users	335	174	51.9	22	6.6	196	58.5	23	11.7	73	37.2	19	9.7	81	41.3
Sotalol															
Incidences	274	109	39.8	20	7.3	129	47.1	35	27.1	50	38.8	23	17.8	21	16.3
Incident users	246	101	41.1	20	8.1	121	49.2	33	27.3	45	37.2	22	18.2	21	17.4
Propranolol															
Incidences	250	130	52	31	12.4	161	64.4	30	18.6	58	36.1	33	20.5	40	24.8
Incident users	226	121	53.5	31	13.7	152	67.2	29	19.1	54	35.5	32	21.1	37	24.3
Nebivolol															
Incidences	62	34	54.8	5	8.1	39	62.9	1	2.6	16	41	2	5.1	20	51.3
Incident users	55	31	56.4	5	9.1	36	65.5	1	2.8	15	41.7	2	5.6	18	50
Carvedilol															
Incidences	29	14	48.3	0	0	14	48.3	1	7.2	5	35.7	1	7.1	7	50
Incident users	26	14	53.8	0	0	14	53.8	1	7.2	5	35.7	1	7.1	7	50
Total alternative beta-blockers															
Incidences*	1518	647	40.8	135	8.9	782	49.7	170	21.7	260	33.2	127	16.2	225	28.8
Incident users[#]	1359	610	44.9	134	9.8	744	54.7	166	22.3	244	32.8	124	16.7	210	28.2

DDI, drug–drug interaction.
*Incidences defined as overlapping prescription of antidepressants and beta-blockers.
[#]Incident users defined as patients who have the incidences.

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Table 4. Proportion of beta-blocker–paroxetine/fluoxetine co-prescriptions

Drugs	Combination of fluoxetine														
		Fluoxetine first		Same start date		Total fluoxetine co-dispensed with beta-blockers		DDI alert system							
								Pharmabase				G-Standard			
	N	*n*	%	*n*	%	*n*	%	Before 2005		2005 and after		Before 2005		2005 and after	
								n	%	*n*	%	*n*	%	*n*	%
Signalled combination															
Metoprolol															
Incidences*	310	120	38.7	33	10.6	153	49.3	31	20.3	66	43.1	22	14.4	34	22.2
Incident Users#	279	105	37.6	33	11.8	138	49.5	29	21.0	61	44.2	17	12.3	32	23.2
Non-signalled combination															
Alternative beta-blockers															
Atenolol															
Incidences	119	37	31.1	15	12.6	52	43.7	21	40.4	7	13.4	12	23.1	12	23.1
Incident users	103	36	34.9	15	14.6	51	49.5	21	41.2	6	11.7	12	23.5	12	23.5
Bisoprolol															
Incidences	85	47	55.3	6	7.1	53	62.4	7	13.2	18	34	8	15.1	20	37.7
Incident users	74	43	58.1	6	8.1	49	66.2	7	14.3	18	36.7	8	16.3	16	32.7
Sotalol															
Incidences	57	21	36.8	2	3.5	23	40.3	9	39.2	7	30.4	4	17.4	3	13
Incident users	48	19	39.6	2	4.2	21	43.8	9	42.8	6	28.6	4	19.1	2	9.5
Propranolol															
Incidences	62	31	50	7	11.3	38	61.3	9	23.7	9	23.7	10	26.3	10	26.3
Incident users	48	27	56.2	7	14.6	34	70.8	9	26.5	8	23.5	9	26.5	8	23.5
Nebivolol															
Incidences	15	8	53.3	1	6.7	9	60	1	11.1	2	22.2	3	33.3	3	33.3
Incident users	10	7	70	1	10	8	80	1	12.5	1	12.5	3	37.5	3	37.5
Carvedilol															
Incidences	16	7	43.7	2	12.5	9	56.2	4	44.5	3	33.3	1	11.1	1	11.1
Incident users	13	7	53.8	2	15.4	9	69.2	4	44.5	3	33.3	1	11.1	1	11.1
Total alternative beta-blockers															
Incidences*	354	151	42.6	33	9.3	184	51.9	51	27.7	46	25	38	20.7	49	26.6
Incident users#	296	139	46.9	33	11.2	172	58.1	51	29.7	42	24.4	37	21.5	42	24.4

DDI, drug–drug interaction.
*Incidences defined as overlapping prescription of antidepressants and beta-blockers.
#Incident users defined as patients who have the incidences.

Table 5. Description of mean daily dose expressed as DDD*

	DDD								
	<1			1			>1		
Drug (incident users = *n*)	*n*	%	Mean (SD)	*n*	%	Mean (SD)	*n*	%	Mean (SD)
Metoprolol–paroxetine									
Metoprolol (1482)	1343	90.6	0.47 (0.2)	0	0	0	139	9.4	1.32 (0.3)
Paroxetine (1473)	541	36.7	0.74 (0.2)	602	40.9	1	330	22.4	1.51 (1.3)
Metoprolol–fluoxetine									
Metoprolol (275)	247	89.8	0.47 (0.2)	0	0	0	28	10.2	1.34 (0.3)
Fluoxetine (274)	53	19.3	0.76 (0.2)	144	52.6	1	77	28.1	1.50 (0.4)
Comparators									
Metoprolol without paroxetine and fluoxetine (55 421)	49 521	89.4	0.47 (0.2)	27	0.1	1	5873	10.6	1.36 (0.9)
Paroxetine without metoprolol (6885)	2083	30.3	0.72 (0.2)	3348	48.6	1	1454	21.1	1.48 (0.6)
Fluoxetine without metoprolol (1586)	279	17.6	0.76 (0.2)	911	57.4	1	396	25	1.59 (0.6)

*DDD stands for defined daily dose.

DISCUSSION

Exposure to metoprolol–paroxetine/fluoxetine combinations, a CYP2D6-mediated DDI, continues to be observed among the elderly (2039 incidences). This large number could result in considerable DDI-related health and economic burdens.[44,45] Our results are in line with other studies. Preskorn *et al.* reported that paroxetine/fluoxetine users frequently receive CYP2D6 substrates.[46] A similar report from Norway found that paroxetine/fluoxetine and metoprolol were often co-administered simultaneously.[47] However, these studies involved shorter observation periods and smaller populations than those covered in our database. Metoprolol–paroxetine/fluoxetine co-medication appears to be common because of the clinical relationship between cardiovascular disease and depression.[17]

Around 57.3% of metoprolol–paroxetine/fluoxetine precriptions were signalled by the DDI alert systems: G-Standard and Pharmabase. This suggests that the alerts were overlooked or deemed clinically irrelevant by clinicians and pharmacists. Van der Sijs *et al.* reported comparable findings for a Dutch university medical centre, stating that the metoprolol–CYP2D6 inhibitor combination is one of the most commonly overridden DDI alerts.[48] Some patients had several incidences, indicating that DDI alerts were ignored several times. This is supported by a previous study which found that DDI warnings on renewed prescriptions tend to be overridden.[49]

The DDI of metoprolol–paroxetine/fluoxetine is considered pharmacokinetically important. Some studies suggest that fluoxetine/paroxetine could increase the area under curve value of metoprolol substantially.[15,50,51] However, there is disagreement on the effects of this DDI. Some case studies report the adverse effects of metoprolol–paroxetine/fluoxetine co-administration. The inhibition of metoprolol metabolism by fluoxetine induced undesirable bradycardia.[25] The same side effect was reported related to paroxetine–metoprolol co-adminstration.[13] Onalan *et al.* reported a more severe case, an atrioventricular block, in an elderly woman using paroxetine and metoprolol concurrently.[26] But other studies involving more patients reported different results. No significant side effects were reported by 17 depressed acute myocardial infarction patients treated with metoprolol–paroxetine, except for two patients who needed dose adjustment for metoprolol because of bradycardia and orthostatic hypotension.[21] Consistent with this finding, Kurdyak *et al.* described that adding a strong CYP2D6 inhibitor (paroxetine and fluoxetine) for elderly patients using metoprolol did not alter the risk of bradycardia compared to non-potent CYP2D6 inhibitors.[22] Perhaps, the DDI is ignored because of these conflicting reports. Taylor *et al.* described that practitioners tend to override DDIs which they are familiar with and they assume do not produce clinically relevant side effects.[52,53]

In this study, we estimated that a larger proportion of metoprolol users was co-prescribed with alternative antidepressants than paroxetine/fluoxetine. Citalopram was the most common replacement therapy co-dispensed with metoprolol. After exceeding the number of combined paroxetine–metoprolol prescriptions in 2004, citalopram–metoprolol use fell briefly as paroxetine–metoprolol combination increased again in 2005. This can be explained by the above mentioned decision at Pharmabase not to signal the

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paroxetine/fluoxetine–metoprolol combination because of the conflicting reports on its clinical relevance. The impact of this DDI alert system change is also clearly evidenced by the increase of paroxetine/fluoxetine–metoprolol co-prescription screened by Pharmabase from 2005. Metoprolol–citalopram was consistently the most commonly prescribed drug combination from 2008. The same results were reported for the Swedish population, where more patients used citalopram/sertraline–metoprolol co-prescription (29 058) than metoprolol–paroxetine/fluoxetine (3164) from January to April 2008.[54]

The strength of the CYP2D6 inhibition by SSRIs differs, with paroxetine and fluoxetine being the most potent inhibitors.[23,55] They do not differ clinically in their efficacy, safety and tolerability.[56,57] Therefore, if considered clinically relevant, adherence to the 'replace CYP2D6 inhibitor' recommendation should be improved in clinical practice.

The affinity of beta-blockers for CYP2D6 varies, with metoprolol being the most extensively metabolized by this polymorphic enzyme.[58] Overall, the number of paroxetine users co-prescribed with alternative beta-blockers was comparable to the numbers of paroxetine/fluoxetine combined with metoprolol. We found that metoprolol is still the most commonly prescribed beta-blocker in community pharmacies, and the most common alternative beta-blockers co-prescribed with paroxetine/fluoxetine were atenolol and bisoprolol. This is reasonable because metoprolol has been the preferred beta-blocker in clinical practice since the publication of Carlberg B *et al.* in 2004.[59] The Dutch General Practice guidelines also confirm the status of metoprolol.[60] Although the current guidelines also mention other beta-blockers, general practitioners in the Netherlands have most experience with metoprolol and probably prescribe what they are familiar with.

Overall, switching paroxetine/fluoxetine–metoprolol with alternative drugs was rarely observed. This indicates that only a small proportion of patients experienced problems when they were prescribed the combination. This could be because metoprolol is co-prescribed in low doses (mean DDD 0.47). However, we may not conclude less than 1 DDD metoprolol was prescribed because of the presence of paroxetine/fluoxetine, because most metoprolol users received comparably low doses, regardless whether it was co-prescribed. The reduced dose may be due to the patients' high age. Furthermore, the low metoprolol dosage may make it unnecessary to alter the paroxetine/fluoxetine, as observed in this study.

The last recommendation in the guideline is to inform patients about the DDI's potential side effects. However, we were unable to assess whether pharmacists adhered to this recommendation. We did not perform a survey of the extent to which pharmacies were aware of this interaction and gave sufficient information to patients. Follow-up studies should, therefore, be performed.

Our study has some limitations. First, we did not have information about the adverse events experienced by each patient and did not determine the outcomes of pharmacotherapy. This is because our study assesses the DDI burden, not its outcomes. Second, we did not check the plasma concentration of metoprolol in patients, meaning that we cannot confirm an increased area under curve value. Third, we did not obtain information on the patients' entire drug regimen. Elderly patients with polypharmacy may be prescribed other drugs affecting two or more CYP enzymes, thus requiring a more advanced recommendation.[29] Fourth, we did not have information about each patient's CYP2D6 genotype and phenotype. Polymorphism may have implications on recommendations to manage the interactions.[14,16,55,61] People with a variant CYP2D6 genotype may be differently affected by metoprolol–paroxetine/fluoxetine co-medication because the inhibition of CYP2D6 by paroxetine/fluoxetine depends on the CYP2D6 status.[23] Finally, as metoprolol dose is assessed using the mean DDD, we could not investigate the dose adjustment per patient.

In general, the management of CYP2D6-mediated DDI remains suboptimal. The incorporation of DDIs with debatable clinical relevance gives rise to an abundance of alerts and leads to alerts being overridden.[62] Efforts to increase the specificity of DDI alerts by understanding DDI burden and adding information regarding their clinical relevance should be encouraged.[48] Adherence to the guidelines could also be enhanced by increasing the role of the pharmacist in responding to DDI alerts.[63,64] Because the co-medication of metoprolol–paroxetine/fluoxetine is still observed, a decision should be made whether the interaction is deemed sufficiently clinically significant to keep it in both surveillance systems, G-Standard and Pharmabase. Therefore, the clinical impact of the combination at the population level should be investigated.

CONFLICT OF INTEREST

Sander D. Borgsteede is employed at Health Base Foundation (HBF), an independent, non-commercial foundation, that maintains a drug information database

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(Pharmabase) and supports health care professional with a clinical decision support system. The interaction studied in this manuscript is subject to medical information provided by HBF. HBF has a scientific, non-commercial interest in the products being studied.

KEY POINTS

- CYP2D6-based drug–drug interactions are still observed in the elderly population regardless of the presence of a drug–drug interaction alert surveillance tool.
- Of metoprolol users, the number of patients dispensed with an alternative antidepressant is higher than those with paroxetine/fluoxetine prescriptions.
- The number of paroxetine/fluoxetine users who were co-prescribed metoprolol was comparable with the number who were co-medicated with alternative beta-blockers.
- Once a metoprolol–paroxetine/fluoxetine or reverse combination is started, the co-medication is hardly ever switched to a non-interacting drug.
- Of the elderly who use metoprolol with or without paroxetine/fluoxetine, about 90% use a low dose.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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