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Drug Interactions in Dying Patients
A Retrospective Analysis of Hospice Inpatients in Germany

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Abstract

Background: Patients at the end of life often receive numerous medications for symptom management. In contrast to all other clinical situations, the aim of pharmacotherapy is strictly focused on quality of life.

Objective: The primary aims of this study were to assess the potential for drug-drug interactions (DDIs) in patients at the very end of life by identifying drug combinations and risk factors associated with a high risk of DDIs; and evaluate the clinical relevance of the potential DDIs in this unique patient population. Secondary objectives were to increase prescriber awareness and to derive a comprehensive framework for physicians to minimize DDIs in this specific setting of end-of-life care.

Materials and Methods: Charts of 364 imminently dying inpatients of two hospices were reviewed retrospectively. Drugs prescribed during the last 2 weeks of life were screened for DDIs by the electronic database of the Federal Union of German Associations of Pharmacists, which classifies DDIs by therapeutic measures required to reduce possible adverse events according to the ORCA system (OpeRational ClAssification of Drug Interactions).

Results: Potential DDIs were detected in 223 patients (61%). In a multivariate analysis, polypharmacy was the major predictor for DDIs (odds ratio 1.5, 95% CI 1.4, 1.6). The drugs most commonly involved in therapeutically relevant potential DDIs were antipsychotics, antiemetics (e.g. metoclopramide, antihistamines), antidepressants, insulin, glucocorticoids, cardiovascular drugs and, in particular, NSAIDs. The most prevalent potential adverse effects were pharmacodynamically additive anticholinergic, antidopaminergic, cardiac (QT interval prolongation) and NSAID-associated toxicity (e.g. gastrointestinal, renal).

Conclusion: In the context of end-of-life care, the clinical relevance of DDIs differs from other clinical settings. Most DDIs can be prevented if the prescribing physician considers a few therapeutic principles. Specifically, this concerns the awareness of futile and high-risk medications, as well as rational alternatives.

Background

Potential drug-drug interactions (DDIs) and their clinical relevance have been addressed in various oncology settings,[1-5] and the importance of DDIs in palliative care has been enlightened in an extensive review.[6] Moreover, two preceding studies assessed DDIs in cancer patients who did not receive any more disease-modifying therapy: (i) our working group assessed potential DDIs in inpatients on a palliative care unit;[7] and (ii) Riechelmann et al.[8] investigated potential DDIs in outpatients attending palliative care clinics. However, such information is not available for imminently dying patients in the last days of life. In this specific setting, pharmacotherapy exclusively aims at quality of life (QOL), while outcomes that are commonly used in DDI studies, such as long-term morbidity, mortality or resource utilization, if at all, play a minor role in therapeutic decisions.[5,9-11] Therefore, a retrospective study that assessed the potential for DDIs of patients dying in inpatient hospices with a clear focus on the impact on QOL was performed. The study aims to (i) assess the potential for DDIs in patients at the very end of life by identifying drug combinations and risk factors associated with a high risk of DDIs; and (ii) evaluate the clinical relevance of the potential DDIs in this unique patient population. Secondary objectives are to increase prescriber awareness and to derive a comprehensive framework for physicians to minimize DDIs in this specific setting of end-of-life care.

Materials and Methods

A retrospective systematic analysis of the theoretical potential for DDIs of inpatients of two inpatient hospices in the region around Cologne, Germany, was performed. The Ethics Committee responsible for our institution did not have any objections concerning this evaluation since data processing concerned routine anonymised clinical data and was performed retrospectively.

Setting

Since the terminology around palliative and hospice care has developed differently around the globe,[12] the assignments and structure of German inpatient hospices have to be described. Hospice care generally describes a holistic approach of palliative care for patients in the last phase of an incurable disease through the treatment of physical, emotional, social and spiritual needs.[13] Hospice care can be provided at home or at inpatient facilities. In the US, the term hospice is usually used for homecare that can be assisted by inpatient hospice facilities.[14] These inpatient hospices supply short-term inpatient care with the aim of discharging the patient back into home-based hospice care.[15] In contrast, in Germany the term hospice is used for specialized inpatient facilities that provide terminal care for dying patients in the terminal phase of an incurable disease if the patients cannot be adequately cared for at home, but inpatient treatment in an acute-care hospital (e.g. on a palliative care inpatient unit) is not required.[16] Care is provided by specialized palliative care nurses and volunteers. A physician is not present at all times and physician services are provided by family doctors on an as-needed basis.[16] Patients usually stay less than 4 weeks in these inpatient hospices until they die, but length of stay varies and may also be in the magnitude of several month in rare cases. Hospices have to be clearly distinguished from inpatient palliative care units. Palliative care units are part of a hospital delivering palliative care by a multiprofessional team to acutely medically deteriorated patients with the aim of improving or stabilizing the patient's clinical situation and to discharge the patient home or to an inpatient hospice.[16,17]

Study Design

Medical records of all 364 patients (237 in hospice 1, 127 in hospice 2) cared for between July 2006 and November 2010 and who died in inpatient hospices were assessed. Information about demographic data, underlying disease, and medication was obtained from the records. In accordance with our previous study,[7] the aim was to identify the entire theoretical potential for DDIs in this specific setting of care. Therefore, the drugs included in the analysis were all drugs that had been prescribed to a patient only in the

last 2 weeks of life (for patients with a minimum length of stay of 2 weeks) or less (if patient's stay until death was shorter than 2 weeks), comprising regular and on-demand or 'rescue' medication. Note that drugs were included if they had been administered to patients or if they had been prescribed in advance (e.g. as a 'rescue' medication) but not administered because they potentially could have been administered at a later time without further assessments. For fixed-dose combinations (e.g. enalapril plus hydrochlorothiazide), each active agent was analysed individually. If a drug was prescribed twice in one patient in different schedules (e.g. long-acting and short-acting morphine), the drug was counted only once.

Table I. Potential for drug-drug interactions

ABDA class	DDI reports [n_i (%)]	Patients affected [n_p (% of 364)]
1 Contraindicated (serious events likely)	0 (0)	0 (0)
2 Contraindicated as a precaution	18 (2.3)	15 (4.1)
3 Monitoring or adjustment necessary	354 (44.5)	157 (43.1)
4 Monitoring or adjustment necessary in certain cases	47 (5.9)	5 (1.4)
5 Monitor as a precaution	375 (47.1)	164 (45.1)
6 No measures required	2 (0.3)	1 (0.3)
Total number of potential DDIs	796 (100)	223 (61.3)

ABDA = Federal Union of German Associations of Pharmacists; **DDI** = drug-drug interactions; n_i = number of potential interactions; n_p = number of patients.

Drug-Drug Interaction Identification and Classification

Potential DDIs were identified and classified by the database and evaluation software of the Federal Union of German Associations of Pharmacists (ABDA).

For 30 years electronic databases have aimed to facilitate the detection of avoidable DDI-related adverse events. However, the number of known interactions has grown considerably, and thus the results are unspecific excessive lists of medication alerts with no clear focus on clinically relevant DDIs and appropriate decisions, which in turn raises the risk of 'alert fatigue'.[18] Accordingly, recent studies demonstrated that between 69% and approximately 91% of medication alerts were overridden since physicians considered the alerts not to be relevant.[19,20] To overcome this obstacle, current developments of electronic DDI databases have focused on the establishment of a system that classifies potential DDIs not merely according to pharmacological aspects but rather to clinical therapeutic recommendations for their management. This approach has been implemented by the OpeRational ClAssification of Drug Interactions (ORCA) system which was developed by the Drug Interaction Foundation.[21] The system was incorporated into the new database of the ABDA, which has been available since 2009 and implemented in every German pharmacy.[22] It is updated biweekly by two pharmacists who include the newest publications, latest recommendations of healthcare authorities or medical associations, and information from grey literature. The ABDA system classifies potential DDIs by therapeutic recommendations and measures required to reduce possible adverse events into six classes (table I).[22] Moreover, for each identified DDI it provides a monograph with specific information on expected adverse outcomes, underlying mechanisms of interaction (e.g. pharmacokinetic, pharmacodynamic, etc.), management recommendations and recent literature. In particular, class 1–4 DDIs are regarded as clinically and therapeutically relevant,[22] and hence only these were considered for detailed analysis. The analysis was performed in January 2011 and repeated in August 2011 for actuality.

Red, Yellow and Green Flagging

In accordance with our previous study,[7] a ratio (flag score) was calculated to distinguish the potential of the respective substance for DDIs: each time a drug was involved in a DDI that would have required therapeutic action (classes 1–4) due to the database output, e.g. monitoring the patient for the potentially hazardous effects of a likely DDI, it was given one point. The total number of points was then divided by the number of patients who had been prescribed the drug. This ratio was then used as a comprehensive

indicator for the likelihood of generating relevant DDIs when prescribing this drug in the clinical context evaluated below:

'Red flag': flag score ≥50 – beware of therapeutically relevant DDIs, avoid if possible.

'Yellow flag': flag score 25–50 – consider alternatives/discontinuation if possible.

'Green flag': flag score 0–25 – no serious clinical events due to DDIs expected in general.

Statistical Analysis

Microsoft Excel® 2007 (Microsoft Corporation, Redmond, WA, USA) and PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) were used for data analysis. Summary statistics describe demography, frequencies of prescribed drugs and frequencies of potential DDIs. The number of medications per patient and the number of potential DDIs per patient was summed up. Binary logistic regression was used to identify factors associated with a high potential for DDIs: the potential for DDIs was the dichotomous-dependent variable, defined as at least one instance of a theoretical class 1–4 DDI. Age, sex, underlying disease, presence of metastasis and specifically the number of medications were explanatory variables in this model. These possible predictors were tested in univariate and adjusted multivariate analysis. Statistical significance was determined by the Wald Chi-squared test. For nominal and binary variables, the largest subgroup represented respectively the reference. Moreover, univariate analysis was done with logistic regression models for all substances labelled with red or yellow flags to determine predictability of their association with potential class 1–4 DDIs. Statistical significance was set at a p-value <0.05; 95% confidence intervals (CIs) were calculated for proportions and odds ratios (ORs). The complementary part of the patient group that was not exposed to the respective risk served as comparators to determine the ORs.

Table II. Demographics

Characteristic	
Total number of patients [n (%)]	364 (100)
Age (median) [n (range)]	74 (36–99)
Sex [n (%)]	
Female	198 (54)
Male	166 (46)
Underlying disease [n (%)]	
Cancer	342 (94)
Lung	73 (20)
Gastrointestinal	65 (18)
Genitourinary	55 (15)
Breast	29 (8)
Pancreas	27 (7)
Brain	26 (7)
Head and neck	19 (5)
Haematological	12 (3)
Other	36 (10)
Non-cancer	18 (5)
Unknown	4 (1)
Length of stay (days; median) [n (range)]	11 (0–669)
Number of prescribed drugs per patient [n (range)]	
Overall (median)	10 (1–24)
Regular (median)	6 (0–17)
On-demand (median)	5 (0–12)
Most frequent drugs prescribed [n (%)]	
Morphine	314 (86)
Lorazepam	285 (78)
Dipyrone (metamizole)	243 (67)
Fentanyl	168 (46)
Metoclopramide	166 (46)
Macrogol	161 (44)
Dexamethasone	134 (37)
Pantoprazole	90 (25)
Diazepam	87 (24)
Omeprazole	82 (23)
Haloperidol	80 (22)
Sodium picosulfate	76 (21)
Torasemide	72 (20)
Dimenhydrinate	66 (18)
Midazolam	59 (16)

Results

Demography and Medication

Table II describes the characteristics of the 364 patients. The median age was 74 years; half of the patients were between 66 and 81 years of age. The most frequent underlying disease was solid cancer (342 patients; 94%), most often lung cancer (73 patients; 20%). Non-oncological diseases accounted only for 5% (18 patients). The interval

between admission and death was less or equal to 5 days in 35% of patients, less or equal to 2 weeks in 59%, less or equal to 4 weeks in 74%, and consequently in 26% of patients more than 4 weeks. Median length of stay was 11 days compared to an arithmetic mean of 27 days due to the skewed distribution. The most common drugs prescribed to the patient during the last 2 weeks of life were morphine (314 patients; 86%), lorazepam (285 patients; 78%) and dipyrone (243 patients; 67%) [table II]. The median number of total drugs prescribed to each patient was 10 (range 1–24).

Potential Drug Interactions

Potential DDIs affected 223 patients (61% [95% CI 56, 66]) [table I]. The median number of potential DDIs per patient was 1 (range 0–19). The ABDA system reported 796 theoretically possible DDIs in 286 different drug-drug combinations for these 223 patients. Of these 796 DDI reports, 419 (53%) were 'therapeutically relevant' (class 1–4) and affected 167 patients (46% [95% CI 41, 46]). The most common underlying mechanism of the class 1–4 interactions was pharmacodynamic (369 DDIs; 88%).

In univariate and adjusted multivariate analysis, the major factor that significantly predicted the potential for class 1–4 DDIs was the increasing number of medications (polypharmacy): OR 1.47; 95% CI 1.35, 1.61; $p < 0.001$. Logistic regression did not identify any other risk factors that are clinically and statistically significantly associated with increasing the risk for potential DDIs, i.e. sex ($p = 0.131$), age ($p = 0.825$), underlying disease ($p = 0.459$) or presence of metastasis ($p = 0.449$).

No class 1 DDIs (recommendation: contraindicated) but five different class 2 DDIs (recommendation: contraindicated as a precaution) were identified (table III). Class 3 DDIs (recommendation: monitoring or adjustment necessary) affected 157 (43%) patients; the drugs most commonly involved in these DDIs were antipsychotics, dopamine antagonists (e.g. metoclopramide), antihistamines (e.g. dimenhydrinate), tricyclic antidepressants (TCAs, e.g. amitriptyline), NSAIDs (e.g. ibuprofen) and glucocorticoids (e.g. dexamethasone) [table III]. Of a total of 47 reports of class 4 DDIs (recommendation: monitoring or adjustment necessary in certain cases), 43 reports (91%) involved NSAIDs (table III), which were prescribed to a total of 49 patients.

The substances prescribed to at least 5% of patients ($n = 18$) were classified according to the flag score to distinguish substances with a high ('red flag') or a moderate ('yellow flag') potential for DDIs from those with a low potential of DDIs in the specific setting of end-of-life care (tables IV and V). For substances labelled with red or yellow flags, table IV presents the odds of being exposed to at least one potentially relevant DDI for patients to whom the substance was prescribed compared with those to whom it was not prescribed (e.g. the odds of being exposed to a potentially relevant DDI were 14-fold greater for patients receiving ibuprofen than for patients not receiving ibuprofen).

Discussion

This is the first study assessing the potential for DDIs in imminently dying patients who do not require inpatient treatment at an acute care hospital. Similar to our previous study on DDIs of an inpatient palliative care unit in acutely ill patients,[7] the prevalence of potential DDIs in this study is also very high, affecting 60% of patients. While studies from other patient populations and clinical settings focus on mortality and morbidity (e.g. DDI as causes of hospital admissions) associated with DDIs, this study has to discuss the findings in the special clinical setting of patients near end of life when life-prolonging treatment does only play a marginal role (if at all). In the following sections, polypharmacy as the main risk factor for DDI, and the most frequent potentially interacting drug combinations (table III) are discussed in respect of their clinical and therapeutic relevance in order to derive recommendations for making rational therapeutic decisions in this setting of end-of-life care.

Polypharmacy

As in many other studies assessing the potential and predictors for DDIs and associated adverse drug reactions, polypharmacy was identified as a

Table III. Overview of the most common identified class 1–4 drug-drug interactions

Class	ABDA database combination[a]	DDI reports [n_i (% of 796)]	Patients affected [n_p (% of 364)]	Underlying mechanism	Expected adverse outcomes
1	No class 1 DDIs detected				
2	Opioid agonists (e.g. morphine)/opioid partial agonists (e.g. buprenorphine)	8 (1.0)	5 (1.4)	Pharmacodynamic, inhibition of opioid receptors	Reduced analgesic effects, withdrawal syndrome possible
	Dopamine antagonists (e.g. metoclopramide)/levodopa	5 (0.6)	5 (1.4)	Pharmacodynamic, antagonistic effects	Reciprocal reduced efficacy, deterioration of Parkinson's disease symptoms
	Proton pump inhibitors (e.g. omeprazole)/clopidogrel	2 (0.3)	2 (0.5)	Pharmacokinetic, CYP inhibition by PPIs	Reduced anticoagulant efficacy with an increased risk of infarctions; apparently no significant role in end-of-life care
	Midazolam/carbamazepine	2 (0.3)	2 (0.5)	Pharmacokinetic, induction of CYP3A enzymes	Reduced sedative effects of midazolam
	Histamine H_1-blockers (e.g. dimenhydrinate)/antiarrhythmic agents (e.g. sotalol)	1 (0.1)	1 (0.3)	Pharmacodynamic, positive addition of adverse effects	Increased risk of VT (torsades de pointes) due to QT interval prolongation; in end-of-life care, this is only relevant in case of symptomatic arrhythmias
3	Dopamine antagonists (e.g. metoclopramide)/antipsychotics (e.g. haloperidol)	76 (9.5)	65 (17.9)	Pharmacodynamic, positive addition of adverse effects	Increased extrapyramidal adverse effects
	TCAs and analogues (e.g. amitriptyline)/antipsychotics (e.g. haloperidol)	42 (5.3)	32 (8.8)	Pharmacodynamic, positive addition of adverse effects	Increased risk of VT due to QT interval prolongation, anticholinergic and sedative adverse effects, especially poor CYP2D6 metabolizers
	H_1-blockers (e.g. dimenhydrinate)/antipsychotics (e.g. haloperidol)	27 (3.4)	25 (6.9)	Pharmacodynamic, positive addition of adverse effects	Increased risk of VT (torsades de pointes) due to QT interval prolongation; in end-of-life care, this is only relevant in case of symptomatic arrhythmias
	NSAIDs (e.g. ibuprofen)/glucocorticoids (e.g. dexamethasone)	26 (3.3)	24 (6.6)	Pharmacodynamic, positive addition of adverse effects	Increased ulcerogenic effects, increased risk of upper gastrointestinal bleedings; potential risks for the patient in end-of-life care need to be assessed (e.g. medical history)
	H_1-blockers (e.g. dimenhydrinate)/TCAs and analogues (e.g. amitriptyline)	19 (2.4)	17 (4.7)	Pharmacodynamic, positive addition of adverse effects	Increased risk of VT (torsades de pointes) due to QT interval prolongation; in end-of-life care, this is only relevant in case of symptomatic arrhythmias
	Antihyperglycaemics (e.g. insulin)/glucocorticoids (e.g. dexamethasone)	17 (2.1)	15 (4.1)	Pharmacodynamic, stimulation of gluconeogenesis	Reduced blood glucose suppressing effects, risk of hyperglycaemia; in end-of-life care, this is only relevant in case of symptomatic hyperglycaemia
	Dopamine antagonists (e.g. metoclopramide)/SSRIs (e.g. citalopram)	11 (1.4)	11 (3.0)	Pharmacodynamic, positive addition of adverse effects	Increased extrapyramidal adverse effects, risk of serotonin syndrome

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Table III. Contd

Class	ABDA database combination[a]	DDI reports [n_i (% of 796)]	Patients affected [n_p (% of 364)]	Underlying mechanism	Expected adverse outcomes
4	NSAIDs (e.g. ibuprofen) in combination with:				The clinical role of the following DDIs within this class needs to be assessed individually in the setting of end-of-life care (see the Polypharmacy and NSAID Combinations sections):
	kaliuretic diuretics (e.g. torasemide)	21 (2.6)	18 (4.9)	Pharmacodynamic, increased vascular tone	decreased diuretic and hypotensive effects
	ACE inhibitors (e.g. ramipril)	7 (0.9)	7 (1.9)	Pharmacodynamic, increased vascular tone	decreased hypotensive effects and increased risk of renal impairment
	potassium-sparing diuretics (e.g. spironolactone)	6 (0.8)	6 (1.6)	Pharmacodynamic, inhibition of prostaglandin synthesis	hyperkalaemia and renal failure
	β-blockers (e.g. bisoprolol)	5 (0.6)	5 (1.4)	Pharmacodynamic, effect unknown	decreased hypotensive effects
	angiotensin II receptor antagonists (e.g. valsartan)	3 (0.4)	3 (0.8)	Pharmacodynamic, increased vascular tone	decreased hypotensive effects

a The following DDIs are presented: class 1 and 2 – every DDI that was found; class 3 – DDIs that affected at least ten patients; class 4 – NSAID combinations that affected at least three patients.

ABDA = Federal Union of German Associations of Pharmacists; **CYP** = cytochrome P450 enzymes; **DDIs** = drug-drug interactions; n_i = number of interactions; n_p = number of patients; **PPIs** = proton pump inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants; **VT** = ventricular tachycardia.

major risk factor.[1,4,8,9] Patients with terminal illness often suffer from a variety of symptoms that require a number of different medications for their management. As pharmacotherapy in end-of-life care should focus on the patient's best possible QOL, drugs for the prevention or modification of primary or secondary diseases are usually inappropriate, since their benefits are outweighed by potential adverse drug events such as DDIs that would impair QOL,[23] and the time to clinical benefit exceeds life expectancy.[24] Two recent studies pointed out that, in particular, patients at the end of life take numerous futile medications that lack short-term benefits.[25,26] Therefore, this study affirms the recommendation of other authors that, specifically, cardiovascular (e.g. β-blocker, ACE inhibitors, angiotensin II receptor antagonists, diuretics, etc.), respiratory (theophylline), oral anti-diabetic (e.g. metformin) and antiplatelet (e.g. clopidogrel) drugs should be avoided in these patients[23] since all these drugs were involved in several potential DDIs in our population. Although not all of these DDIs are relevant for dying patients as discussed hereinafter, the avoidance of these drugs is worthwhile, especially with respect to adverse drug effects in general.

Interacting Drug Combinations

Opioid Agonists (e.g. Morphine)/Opioid Partial Agonists (e.g. Buprenorphine)

The ABDA database reported this combination as a class 2 DDI based on theoretic pharmacological considerations, case reports[27] and small studies with opiate-dependent volunteers.[28] However, recently a randomized controlled trial and a review contradict the ABDA recommendation.[29,30] In practice, the drug combination neither led to a reduction of analgesia nor to sedative adverse effects.[29] This strengthens the hypothesis of our earlier publication that favours the critical reflection of DDI database alerts by experienced physicians and pharmacists.[7]

Dopamine Antagonists (e.g. Metoclopramide)/Levodopa

As stated in studies addressing symptom management of neurological patients, the co-

Table IV. Substances with a high and moderate potential for drug interactions ('red and yellow flags') ordered by flag score

Drug	Patients affected [n_p (% of 364)]	DDI classes 1–4 (n_i)	Flag score[a]	OR (95% CI)	p-Value[b]
Red Flags					
Ibuprofen	23 (6.3)	39	169.6	14.0 (3.2, 60.8)	<0.001
Haloperidol	80 (22.0)	97	121.3	6.4 (3.6, 11.5)	<0.001
Amitriptyline	44 (12.1)	46	104.5	3.7 (1.8, 7.4)	<0.001
Insulin	22 (6.0)	23	104.5	5.8 (1.9, 17.6)	0.002
Promethazine	26 (7.1)	21	80.8	2.0 (0.9, 4.5)	0.102
Levomepromazine	34 (9.3)	25	73.5	3.1 (1.5, 6.8)	0.004
Dimenhydrinate	66 (18.1)	48	72.7	2.6 (1.5, 4.8)	0.001
Citalopram	21 (5.8)	15	71.4	2.0 (0.8, 4.9)	0.135
Metoclopramide	166 (45.6)	89	53.6	3.6 (2.3, 5.5)	<0.001
Yellow Flags					
Spironolactone	23 (6.3)	11	47.8	1.9 (0.8, 4.5)	0.142
Scopolamine	20 (5.5)	8	40.0	2.3 (0.9, 5.9)	0.085
Ramipril	22 (6.0)	8	36.4	2.2 (0.9, 5.3)	0.091
Bisoprolol	37 (10.2)	12	32.4	1.3 (0.6, 2.5)	0.482
Dexamethasone	134 (36.8)	41	30.6	2.2 (1.4, 3.4)	<0.001
Torasemide	72 (19.8)	18	25.0	4.0 (2.3, 7.1)	<0.001
Hydrochlorothiazide	20 (5.5)	5	25.0	2.9 (1.1, 7.8)	0.032

a Flag score: number of class 1–4 DDIs per patients exposed (ratio $n_i/n_p \times 100$).

b p-Value determined by Wald Chi-squared test.

DDIs = drug-drug interactions; n_i = number of interactions; n_p = number of patients; **OR** = odds ratio for the potential of class 1–4 DDIs in univariate analysis.

administration of centrally acting dopamine agonists and antagonists may be deteriorating to patients with Parkinson's disease and thus reduce significantly their QOL.[31] Other antiemetics should be considered; in particular, domperidone is suggested in order to reduce extrapyramidal adverse effects (as it does not cross the blood-brain barrier) and adverse gastrointestinal effects due to levodopa treatment.[31]

Proton Pump Inhibitors (e.g. Omeprazole)/Clopidogrel

A loss of the efficacy of clopidogrel and thus an increased risk of infarctions is associated with the concomitant administration of proton pump inhibitors other than pantoprazole and clopidogrel via cytochrome P450 (CYP) interactions, in particular with CYP2C19.[32] This class 2 DDI does not play a significant role in end-of-life care since the time-to-benefit of clopidogrel exceeds life expectancy. However, in light of polypharmacy, the discontinuation of clopidogrel and critical reflection of the benefits of omeprazole in this setting can be advised.[23]

Midazolam/Carbamazepine

Carbamazepine is known to frequently interact with other drugs as a result of its CYP enzyme-inducing effects that would decrease the efficacy of midazolam by lowering midazolam serum levels.[33] For antiepileptic therapy, levetiracetam has been recommended as a therapeutic alternative with no evidence for clinically relevant DDIs and high efficacy (non-inferior to carbamazepine).[34] For the treatment of neuropathic pain, pregabalin could be an alternative to carbamazepine since it has been identified as an effective and safe treatment option.[35]

Histamine H_1-Blockers (e.g. Dimenhydrinate)/Antiarrhythmic Agents (e.g. Sotalol)

Both drug classes prolong the QT interval.[36] Burdensome dizziness and fainting or fatal ventricular fibrillation may occur dose-dependently

due to torsades de pointes.[37] Although QT interval prolongation could be monitored by ECG, ECG monitoring is not indicated in end-of-life care following the principles of end-of-life care to provide maximum comfort by the 'high person, low technology' approach.[38] Therefore, as with other publications reporting on QT interval-prolonging drugs in palliative care (e.g. methadone),[39] the risks of their use should be carefully weighed against potential benefits with respect to patients' QOL.

Table V. Substances with a low potential for drug interactions ('green flags')

Drug	Patients affected [n_p (% of 364)]	DDI classes 1–4 (n_i)	Flag score[a] green
Morphine	314 (86.3)	13	4.1
Lorazepam	285 (78.3)	7	2.5
Dipyrone (metamizole)	243 (66.8)	0	0.0
Fentanyl	168 (46.2)	8	4.8
Macrogol	161 (44.2)	0	0.0
Pantoprazole	90 (24.7)	0	0.0
Diazepam	87 (23.9)	4	4.6
Omeprazole	82 (22.5)	2	2.4
Sodium picosulfate	76 (20.9)	0	0.0
Midazolam	59 (16.2)	9	15.3
Bisacodyl	53 (14.6)	0	0.0
Esomeprazole	50 (13.7)	0	0.0
Furosemide	46 (12.6)	4	8.7
Flunitrazepam	42 (11.5)	2	4.8
Zopiclone	37 (10.2)	0	0.0
Butylscopolamine	35 (9.6)	0	0.0
Oxazepam	35 (9.6)	2	5.7
Hydromorphone	33 (9.1)	1	3.0
Ondansetron	33 (9.1)	0	0.0
Acetylcysteine	31 (8.5)	3	9.7
Codeine	30 (8.2)	0	0.0
Levothyroxine	29 (8.0)	4	13.8
Enoxaparin	24 (6.6)	0	0.0
Prednisone	24 (6.6)	4	16.7
Lactulose	21 (5.8)	0	0.0

a Flag score: number of class 1–4 DDIs per patients exposed (ratio $n_i/n_p \times 100$).

DDIs = drug-drug interactions; n_i = number of interactions; n_p = number of patients.

Dopamine Antagonists (e.g. Metoclopramide)/ Antipsychotics (e.g. Haloperidol)

As in other studies assessing palliative care inpatients, this combination was frequent.[7] An additive risk of adverse effects via central dopamine D_2 antagonism in terms of extrapyramidal adverse effects (akathisia, tardive dyskinesia) has to be considered.[40] The concomitantly administered antipsychotics aimed at the relief of nausea or at reducing delirium, disorientation or restlessness. In the former case (antiemetic use), they are usually prescribed at a low dose and the potential for DDIs should be less. Therefore, it might be beneficial to follow an empirical treatment approach especially for patients with severe nausea that addresses various mechanisms by combining the prokinetic and centrally antiemetic effects of these drugs,[41,42] although the evidence for this approach is scarce.[43] Correspondingly, Weschules[44] reported that the fixed combination of both drugs was well tolerated in a number of hospice patients in the management of nausea. In the latter case (antipsychotic use), the potential for DDIs of antipsychotics at a higher dose is high (overall OR for all antipsychotics 6.8; $p < 0.001$) [table IV], but their use in the setting of end-of-life care is often indispensable. On the one hand, the occurrence of potential extrapyramidal adverse effects can be monitored clinically at every patient visit by mere inspection and anamnesis. On the other hand, following the recommendation of authors reporting about pharmacotherapy in Parkinson's disease,[31] the concomitant use can be easily avoided if domperidone is chosen instead of metoclopramide.

Tricyclic Antidepressants (TCAs) and Analogues (e.g. Amitriptyline)/Antipsychotics (e.g. Haloperidol)

Additive cardiotoxic (QT interval prolongation),[45] and in particular anticholinergic and sedative adverse effects,[46] have to be expected when combining TCAs and antipsychotics. Attention should be paid to the exponentially additive effects of multiple drugs with anticholinergic activity even in low doses[7,47] since anticholinergic toxicity and sedative adverse effects are very burdensome with significant impact on QOL even in the last hours of life, as revealed in geriatric

studies.[46] A broad range of adverse effects has to be considered ranging from xerostomia, constipation, urination disorders to neurological disorders such as visual impairment, confusion, sleepiness, delirium and cognitive decline.[47,48] Since ECG is not indicated to monitor cardiotoxic effects [see the Histamine H_1-Blockers (e.g. Dimenhydrinate)/Antiarrhythmic Agents (e.g. Sotalol) section] and the assessment of anticholinergic symptoms in dying patients may be difficult,[7] the indication for this combination should be carefully scrutinized. Generally, findings from this and our previous study[7] support Tune's recommendation[47] to minimize the concomitant use of medications with anticholinergic activity. Particularly in end-of-life care, psychostimulants such as methylphenidate represent alternatives to TCAs to reduce symptoms of depression without delayed onset.[49] Pregabalin represents a safe alternative for the treatment of neuropathic pain that allows for even more effective pain relief.[50]

H_1-Blockers (e.g. Dimenhydrinate)/Antipsychotics (e.g. Haloperidol)

In this case, a dose-dependent prolongation of the QT interval has to be considered.[51] If antipsychotics are used for antiemetic therapy (low dose) this drug combination is a practical approach that combines the antiemetic effects of different agents acting via different receptors, as described in the Dopamine Antagonists (e.g. Metoclopramide/Antipsychotics (e.g. Haloperidol) section.

NSAIDs (e.g. Ibuprofen)/Glucocorticoids (e.g. Dexamethasone)

This well known potential DDI is associated with an increased risk of gastric ulcers and upper gastrointestinal bleeding.[52] While the use of NSAIDs has to raise concerns (see the NSAID Combinations section), glucocorticoids are very often indispensable since they address various symptoms in the setting of palliative care (dyspnoea, nausea, vomiting, fatigue, anorexia and cachexia).[7,53,54] If NSAID use is considered necessary, we suggest discontinuing the corticosteroid by tapering off the dose if the symptoms are well controlled and re-applying a high single morning dose if symptoms arise once more.[7]

H_1-Blockers (e.g. Dimenhydrinate)/TCAs and Analogues (e.g. Amitriptyline)

As described in the Tricyclic Antidepressants (TCAs) and Analogues (e.g. Amitriptyline)/Antipsychotics (e.g. Haloperidol) section, DDI-related anticholinergic, sedative and cardiac toxicities have to be taken into account.[36,46] Rational alternatives for the TCA should be considered [see the Tricyclic Antidepressants and Analogues (e.g. Amitriptyline)/Antipsychotics (e.g. Haloperidol) section].

Antihyperglycaemics (e.g. Insulin)/Glucocorticoids (e.g. Dexamethasone)

Glucocorticoids antagonize the blood glucose-lowering effects of insulin, but negative impacts of elevated blood glucose as a cardiovascular risk factor can be neglected in the setting of hospice care and should not be a reason to discontinue the glucocorticoids, which are often indispensable as described in the NSAIDS (e.g. Ibuprofen)/Glucocorticoids (e.g. Dexamethasone) section. However, insulin should be reduced due to the limited oral uptake of nutrition and, as in the work of Gannon and Dando,[55] we suggest that symptomatic hyperglycaemia can be monitored clinically.

Dopamine Antagonists (e.g. Metoclopramide)/Selective Serotonin Reuptake Inhibitors (e.g. Citalopram)

In psychiatric patients, concomitant treatment with selective serotonin reuptake inhibitors (SSRIs) and metoclopramide has been shown to cause neuropsychiatric toxicity, ranging from extrapyramidal adverse effects (e.g. dystonia) to serotonin syndrome.[56,57] We advise considering alternatives such as domperidone as another prokinetic antiemetic or psychostimulants for SSRIs for short-term relief of depression. Note that there is also a risk of serotonin syndrome when co-administrating some opiate analgesics (e.g. tramadol, methadone and dextromethorphan) with SSRIs.[58]

NSAID Combinations

As in an earlier evaluation from our working group[7] and a recent study assessing the potential DDIs of NSAIDs in the elderly,[59] NSAIDs (e.g. ibuprofen) exhibited the highest potential for DDIs in this study (overall OR for all NSAIDs

including coxibs, except dipyrone and acetaminophen, 11.0; $p < 0.001$) [table IV]. They were involved in several different DDIs in combination with a variety of drugs such as glucocorticoids, SSRIs, diuretics, β-blockers, ACE inhibitors or angiotensin II receptor antagonists (table III). NSAIDs themselves exhibit a broad range of toxicity (gastrointestinal, renal, haematological and cardiovascular) even in short-term use,[60] but the concomitant use of these other drugs leads to pharmacodynamically additive DDIs that may result in excessive toxicity.[59] In a recent review about cancer pain management, Portenoy[61] literally states that the ''high baseline risk related to renal, gastrointestinal, or cardiovascular disease as a strong relative contraindication to NSAID administration''. Considering this recommendation and the conclusion of a Cochrane review that there is only vague evidence to support superior efficacy of combinations of an NSAID with an opioid compared to an opioid alone,[62] the use, benefits and risks of NSAIDs should be scrutinized critically for each patient. Caution is necessary, particularly in patients whose medical history indicates long-term use. As a non-opioid, dipyrone (metamizole) may be a favourable and widely used alternative in countries where it is available,[7] despite the ongoing debate on the incidence of dipyrone-induced agranulocytosis.[60]

Increasing Prescriber Awareness

Implementation of the ORCA system into clinical practice would make it possible to increase prescriber awareness of potentially relevant DDIs. Based on the findings of this study, a concise framework for clinical practice that summarizes the key

Table VI. Main findings and recommendations at a glance

Polypharmacy and futile medications
The indication of any medication at the end of life should be carefully reassessed. The risk of relevant DDIs can be decreased by reducing polypharmacy. Specifically, drugs for primary or secondary disease prevention (e.g. cardiovascular drugs such as ACE inhibitors) can often be discontinued
Pharmacodynamic DDIs
Previous palliative care publications focused on pharmacokinetic DDIs (e.g. related to CYP pathways).[63,64] However, this is our second study that emphasizes the need to heed the more common pharmacodynamic DDIs that were potentially relevant to affecting QOL[7]
Specifically, prescribers should be aware of pharmacodynamically additive toxicity (e.g. antidopaminergic, anticholinergic). Patients with such high-risk (in terms of QOL) combinations should be screened for clinical consequences (e.g. dry mouth if anticholinergic toxicity is likely)
Red flags
Before prescribing the following pharmacological classes of drugs, their individual benefit-risk potential should be critically weighed:
• NSAIDs (including coxibs) exhibit a very high potential for relevant DDIs. Consider alternatives such as dipyrone, the broad range of co-analgesics or simple discontinuation of the drug
• Antipsychotics account for a large number of potential DDIs, but their use is often indispensable. Beware of additive anticholinergic (e.g. constipation) and cardiac (QT interval prolongation) toxicity. Be aware of their dose-dependent potential for DDIs: low in antiemetic use, high in antipsychotic use
• Antiemetics such as dopamine antagonists (e.g. metoclopramide, antipsychotics) and antihistamines are associated with a high potential for relevant DDIs (table IV), especially if combined with each other Domperidone might be a safe alternative as a prokinetic antiemetic to metoclopramide. In refractory nausea, consider 5-HT_3 serotonin antagonists (e.g. ondansetron), which exhibited a safe DDI profile (table V), although they add to the constipating potential of other drugs and their benefit in the palliative care setting is unclear
• Antidepressants such as TCAs and SSRIs are frequently involved in potential DDIs (table IV). Alternatives should be considered with respect to the very limited life expectancy (e.g. psychostimulants)
Green flags
Together with the findings of our previous study,[7] the following substances exhibit a low potential for DDIs in end-of-life care (table V): strong opioids (except methadone), dipyrone, laxatives, proton pump inhibitors, benzodiazepines and zopiclone

CYP = cytochrome P450; **DDIs** = drug-drug interactions; **QOL** = quality of life; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

points (risk factors, pitfalls and recommendations) is provided in order to prevent clinically relevant DDIs in end-of-life care (table VI). Moreover, we agree with the findings of other publications that a close cooperation between the treating physician and an experienced pharmacist with specialized palliative care expertise may be helpful to increase prescriber awareness of DDIs[65] and improve the quality of end-of-life pharmacotherapy.[7,66,67] This in turn should improve patients' QOL.

Limitations

Firstly, the retrospective design to assess theoretically potential DDIs restricts the degree of evidence since we cannot provide information about the number of incidents in which DDIs actually resulted in adverse events. Therefore, we agree with Riechelmann et al.,[1,8] that more research is necessary to clarify the clinical impact of DDIs in palliative and hospice care.

Secondly, generalizability is limited since the substances included in our evaluation were restricted to those administered according to personal experience, institutional routine and national availability; thus, the potential for DDIs of drugs that are used in other countries could not be evaluated. Furthermore, the majority of patients admitted to hospices in Germany are still cancer patients for historical reasons, so that the number of patients with non-cancer diagnoses included in this study is relatively low. One might assume that these patients are prescribed a greater number and variety of drugs for chronic conditions (e.g. congestive heart failure) than cancer patients and are therefore more likely to experience DDIs.

Thirdly, the flag score is not a validated instrument; however, we consider it a valuable tool to describe the potential of the respective substance for DDIs in a specific setting and to increase comprehensibility of the results because it depends on the frequency of prescriptions of a certain drug and the frequency of prescriptions of potential interacting drugs in this specific population. Thus, the potential occurrence of DDIs for a drug given by the flag score is population-specific, although the validity of the relevance of the potential DDIs is limited since the relevance is not population-specific but taken from the database.

Finally, the ABDA database identifies substance-related DDIs irrespective of dose-dependent effects. Therefore, the potential for DDIs will be overestimated to some degree.

Conclusions

The DDI reports of an electronic database should be viewed in the clinical situation of each patient, especially in end-of-life care, since some DDIs were not relevant for this specific population. However, other DDIs bore the risk of seriously jeopardizing QOL even at the end of life. Most of these DDIs can be prevented by considering a few therapeutic principles. Specifically, this concerns the awareness of futile and high-risk medications as well as rational alternatives.

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