Clinically significant drug-drug interactions involving medications used for symptom control in patients with advanced malignant disease. A systematic review.

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Abstract

Context: Most patients with advanced malignant disease need to take several drugs to control symptoms. This treatment raises risks of serious adverse effects and drug-drug interactions (DDIs).

Objectives: To identify studies reporting clinically significant DDIs involving medications used for symptom control, other than opioids used for pain management, in adult patients with advanced malignant disease.

Methods: Systematic review with searches in Embase, MEDLINE and the Cochrane Central Register of Controlled Trials, from the start of the databases (Embase from 1980) through 21st June 2018. In addition, reference lists of relevant full-text papers were hand-searched.

Results: Of 9699 retrieved citations, 462 were considered potentially eligible. After full-text reading, 29 were included in the final analysis, together with 13 papers from reference lists. The 42 included publications were case reports, letters to the Editor and one retrospective study. Drugs most often involved were antiepileptics, antidepressants, corticosteroids and non-opioid analgesics. Clinical manifestations of identified DDIs included sedation, respiratory depression, serotonin syndrome, neuroleptic malignant syndrome, delirium, seizures, ataxia, liver and kidney failure, bleeding, cardiac arrhythmias, rhabdomyolysis and others. The most common mechanisms eliciting DDIs were alteration of CYP450 dependent metabolism and overstimulation of serotonin receptors in the CNS.

Conclusion: Drugs used for symptom control in patients with advanced cancer may cause serious DDIs. Although there is limited evidence for the risk of clinically significant DDIs, physicians treating cancer patients should try to limit polypharmacy,

avoid drug combinations with a high risk of DDIs, and closely monitor patients for adverse drug reactions.

Key words:

Pharmacotherapy; symptoms; cancer patients; palliative care; drug–drug interactions

Running head: Drug interactions of medications used for symptom control

INTRODUCTION

Most patients with advanced malignant disease take drugs to control symptoms. The number and role of drugs used for symptom control usually increase when the patients approach the last days of life (1,2). Additionally, many patients use drugs to treat concomitant diseases, and some continue anticancer medications (3,4). The total number of drugs taken regularly equals or exceeds five, the criterion of polypharmacy, in more than 80% of patients with advanced cancer, and one in four patients take ten or more drugs daily (criterion of hyperpolypharmacy) (3,5,6). This use of multiple medications raises the risk of serious adverse effects caused by drug-drug interactions (DDIs), which may be difficult to adequately diagnose and manage.

Multiple studies have demonstrated that patients with advanced cancer and other palliative care patients, including those in the last days of life, are exposed to a high number of potential DDIs (3,7–12). Published reports on clinically significant DDIs of opioids used for the treatment of pain in cancer patients have been summarized in a systematic review (13). However, clinical reports of significant DDIs of other classes of drugs used for symptom control in cancer patients, as well as of opioids used for the treatment of symptoms other than pain, have not been systematically reviewed.

The aim of the present review is to identify studies reporting clinically significant DDIs involving medications used for symptom control, other than opioids used for pain management, in adult patients with advanced malignant disease.

METHODS

Search strategy

Systematic searches were performed in Embase and MEDLINE through OvidSP, from set up of the databases (Embase from 1980) until June 2018. The last day searched was 21st June 2018. The full search strategy for Embase is presented in supplementary Table 1 (available online). Titles and abstracts of the retrieved citations were reviewed independently by two of the researchers (DFH, AKL), and potentially relevant papers were read in full text (DFH, AKL). In cases of doubt or disagreement, papers were reassessed by all three investigators (DFH, AKL, PK). Additionally, reference lists of all the papers read in full text were hand-searched for relevant papers.

A flow chart showing the selection of included papers is presented in Figure 1.

Figure 1. PRISMA flow chart showing the selection of papers

Inclusion criteria

– Publications reporting clinically significant DDIs involving drugs used for symptom control, excluding opioids used for pain management, in adult patients with advanced malignant disease, as assessed by the authors of the paper (irrespective of whether symptoms were related to cancer or comorbidities)

– Any type of publication: randomized controlled trial, other controlled study, observational study, case report, case series, or letter to the Editor, except for publications available only in abstract form

– Publications in English language

Exclusion criteria

– Experimental studies

– Only pharmacokinetic investigations (no clinical outcome)

Content analysis

The identified publications were grouped according to pharmacological class of drugs involved in the reported DDI, clinical manifestation, and proposed mechanism underlying the DDI. The DDIs and underlying mechanisms were presented according to the interpretations made by the authors of the individual papers. All of the DDIs were assessed using information in Lexicomp Drug Interaction Checker with respect to their severity, risk rating, and level of evidence (14).

RESULTS

Of 9699 retrieved citations, 462 were considered potentially eligible. After full-text reading, 29 were included in the final analysis, together with 13 papers identified through hand-searching of reference lists (Figure 1; Table 1) (15–56). Fifteen of the papers were published in the period 1978–2000, and 27 in the period 2001–June 2018. One of the case reports was supplemented by an erratum (Table 1) (57).

Of the 42 included publications, 30 were case reports presenting one or two relevant patients, 11 were letters to the Editor, and one was a retrospective study reporting four cases. No randomized controlled trials or other controlled studies were identified. In some publications, DDIs in both cancer patients and patients with non-malignant diseases were reported. From these publications, only cases of DDIs in patients with advanced malignant disease were included in the review. In total, the publications reported DDIs in 47 patients.

Of the identified DDIs, 24 (53.3 %) were of major severity, 10 (22.2 %) of moderate severity, and one (2.2%) of minor severity (14). Ten of the DDIs identified (22,2 %) Were not included in the Lexicomp drug-drug interactions database (Tabela 1).

Table 1. Overview of included publications

Drugs used for symptom control involved in DDIs, and clinical manifestations of DDIs

Drugs most often involved were antiepileptics (23 cases) (phenytoin in particular) and antidepressants (10 cases) (mostly selective serotonin reuptake inhibitors). Some DDIs were reported by more than one publication (16,17,20,22,23,25,26,33–35). Twenty publications related to DDIs of symptomatic drugs and oncologic agents (Table 1) (15–32,46,53). The details for all DDIs are given in Table 1.

Most cases of DDIs identified resulted from increased toxicity of the drug used to relieve symptoms or of co-administered drugs. In nine cases, DDIs led to failure of treatment, e.g. the recurrence of seizures in patients treated with an antiepileptic agent.

DDIs involving medications used for symptomatic treatment caused many different clinical manifestations: sedation and coma (20–27,33,40,41,53–55), ataxia (19–25,38,39), serotonin syndrome (42–45,47,49), seizures (28–32,34), liver and kidney failure (15–17,52), respiratory depression/failure (40,41,53–55), delirium (20,23,24,33,39), bleeding (36,56), visual impairment (23,38), cardiac arrhythmias

(48), neuroleptic malignant syndrome (51), rhabdomyolysis (46,50) and others (18,20,26,27,35–38).

Mechanisms underlying DDIs of drugs used for symptom control

Thirty publications identified pharmacokinetic DDIs and eight publications presented pharmacodynamic DDIs. Five publications reported a combination of both pharmacokinetic and pharmacodynamic DDIs (Table 1).

The most common mechanisms eliciting pharmacokinetic DDIs were alteration of drug metabolism (29 studies), including thirteen publications related to inhibition or induction of CYP2C9, CYP3A4 or CYP2C19 izoenzymes of cytochrome P450, and two studies related to glucuronidation. The other mechanisms of pharmacokinetic DDIs were proposed to be secondary to impaired absorption of drugs from the gastrointestinal tract, increased volume of distribution, displacement from protein binding sites, or decreased renal elimination.

Pharmacodynamic DDIs were caused by overstimulation of serotonin receptors in the CNS (five studies), inhibition of prostaglandin synthesis (three studies), as well as other and less clear mechanisms. In some publications, more than one mechanism underlying pharmacokinetic or pharmacodynamic DDIs was proposed (Table 1).

DDIs of non-opioid analgesics

The present review identified only four publications demonstrating DDIs of non-opioid analgesics (15–18). Three publications reported DDIs from combined use of a non-steroidal anti-inflammatory drug and methotrexate or cyclophosphamide. Three

patients using indomethacin experienced methotrexate toxicity manifested as renal failure (16,17), and one patient had a possible DDI of indomethacin and cyclophosphamide that resulted in water intoxication and severe hyponatremia (18). One case report presented a patient with fatal liver toxicity that resulted from concurrent use of acetaminophen, levothyroxine, and sunitinib (15).

DDIs of antiepileptics

Twenty-two publications in the present review concerned antiepileptic drugs (19–40). Eighteen of them referred to phenytoin, and five to other antiepileptic drugs: carbamazepine, valproic acid, and lamotrigine (Table 1). Nine studies reported phenytoin toxicity associated with elevation of its serum concentration above therapeutic range, which manifested as drowsiness, weakness and unsteady gait/ ataxia among other symptoms (19–27). One case reported thrombocytopenia proposed to be secondary to an interaction involving phenytoin, dexamethasone, and cimetidine (35).

In contrast, six cases reported seizures associated with sub-therapeutic serum levels of phenytoin (28–32,34). Three publications presented patients with brain tumors in whom the co-administration of phenytoin and dexamethasone produced diminished efficacy of the treatment, resulting in worsening of the patients' condition, and seizures (32–34). One case report referred to a patient in whom co-administration of warfarin and phenytoin resulted in anticoagulation failure (36).

The remaining reports on DDIs associated with the use of antiepileptics were publications reporting single cases of fatal toxic epidermal necrolysis caused by

combined use of lamotrigine and valproate sodium, carbamazepine toxicity secondary to concurrent use with propoxyphene or terfenadine, and methadone-induced respiratory depression after carbamazepine discontinuation (37–40).

DDIs of antidepressants

Ten publications in the present review reported DDIs of antidepressant medications: citalopram/escitalopram (five studies), sertraline, paroxetine, duloxetine, amitriptyline, trazodone, and nefazodone (one study each) (41–50). Six of these studies reported DDIs resulting in serotonin toxicity in patients with the antidepressant co-administered with medications modifying serotonergic activity in the CNS (opioids, linezolid), or inhibiting the metabolism of citalopram (fluconazole) (42–45,47,49). Two publications presented DDIs of antidepressant drugs manifested as rhabdomyolysis (46,50). One of these cases was believed to be a consequence of co-administration of the SSRI citalopram and irinotecan, two drugs competing for CYP3A4- mediated metabolism. Another case report presented rhabdomyolysis as a consequence of inhibition of simvastatin metabolism secondary to nefazodone, a strong CYP3A4 inhibitor. One publication reported a DDI manifested as opioid overdose in a patient in whom amitriptyline was co-administered with morphine (41). Sertraline combined with midazolam and fentanyl, three substrates of CYP3A4, were also associated with a DDI involving methadone, which led to torsades de pointes (48).

DDIs of antipsychotics

Only two cases of DDIs involving haloperidol were identified in the present review (51,52). One of these publications reported a case of neuroleptic malignant syndrome in a patient who was given haloperidol and fentanyl. Another report presented a possible pharmacokinetic DDI of voriconazole and haloperidol that

resulted in hepatotoxicity in a slow metabolizer of CYP2C19, the major isoenzyme responsible for voriconazole metabolism.

DDIs of corticosteroids

Five of the included publications referred to dexamethasone use (32–36). Four cases related to the concurrent use of the corticosteroid and phenytoin are described above. Two other cases presented pharmacodynamic DDIs of dexamethasone and captopril and acetylsalicylic acid, respectively, which resulted in arterial hypertension and bleeding from gastric ulceration (36).

DDIs of other medications used for symptomatic treatment

We identified seven publications that reported DDIs of other drugs used for symptomatic treatment, including an opioid overdose caused by codeine used for cough concurrently with clarithromycin and voriconazole (54), opioid overdose caused by concurrent use of methadone and cimetidine (55), altered mental status and respiratory failure caused by coadministration of diazepam and idelalisib (53), and two cases of bleeding reported to be secondary to the combined administration of drugs used for symptom control and anticoagulants (omeprazole and warfarin, and loperamide and dabigatran) (36,56). Two cases of DDIs with the possible contribution of cimetidine and midazolam are mentioned above (35,48).

Quality of evidence

The included studies have several limitations. Only case reports, letters to the Editor, and one retrospective study was identified (Table 1). Most of the reports included in this review provided poor level of evidence as judged by Lexicomp Drug Interaction

Checker (14) (28 DDIs (62.2 %) were assessed as having a fair level of evidence, six DDIs (13,3 %) good level of evidence, and only one (2.2 %) excellent evidence). Ten of the DDIs identified (22.2 %) were not included in the drug-drug interactions database (Table 1).

DISCUSSION

Drugs used for symptom control represent multiple classes of medications with variable and complex mechanisms of action and pharmacokinetics. Most of these drugs have potential for serious adverse effects and are known to interact with other medications. Patients with advanced malignant disease are prone to polypharmacy, frequent changes of co-administered drugs and doses, high incidence of organ failure, and numerous symptoms caused by the cancer. All these factors increase the risk for adverse effects due to DDIs. Still, this systematic review showed a limited number of reports of clinically significant DDIs in this patient population. Also, we were not able to find any systematic studies on the risk for such DDIs.

The most frequent drug classes involved were antiepileptics and antidepressants, and the most frequent DDI-related adverse effects were sedation, serotonergic syndrome and other neurologic complications/symptoms, and organ failure. As expected, some DDIs were related to pharmacokinetic interactions, and some to pharmacodynamic synergism or antagonism. Due to the lack of systematically obtained information, the literature can only point towards involved drug classes, symptoms and mechanisms, while no quantification of the importance of each of these factors is possible.

The present review demonstrates that evidence for DDIs of drugs used for symptom control in cancer patients (other than opioids used for pain treatment) is very limited. We identified only case reports, letters to the Editor and one retrospective study (Table 1). This result is consistent with our previously published review on DDIs of opioids used for pain treatment in patients with cancer (13). Seven of the publications included in the present review of drugs used for symptom control were also part of the opioid DDI review, because they concern interactions between opioids used for pain and another drugs used for symptom control. The unexpectedly low number of clinically significant DDIs of drugs used for symptom control is in contrast to the huge number of potential DDIs specified in drug interaction checkers recommended for use in populations of cancer patients and other palliative care patients (7,9–12).

The results of this review demonstrate that current knowledge gives no insight into the actual risk for DDIs in patients with advanced cancer. On the one hand, there is certainly an under-reporting of such incidences, while on the other hand, symptoms in patients using two or more drugs may be caused by other factors than a DDI, e.g. the disease itself, and erroneously be categorized as a DDI. The latter may be true for some of the proposed DDIs in this review, which seem to be less biologically plausible. Other study designs such as prospective observational studies consecutively including patients that have a specific new drug added to an established drug regimen, or including patients in whom one or more drugs are terminated when a certain adverse symptom is observed, are needed. However, even in such studies, it could be difficult to address if adverse effects be related to combining drug A and drug B, or stem from the drugs´ effects, regardless of their co-

administration. In fact, the ideal study would be to compare three groups; drug A alone, drug B alone, and drug A+B, in order to observe if there are any DDI effects. Studies on DDIs would also have to take into consideration genetic determinants affecting the studied interaction. Examples are variants causing poor and rapid CYP2D6 and CYP2C19 metabolizers, reported to cause the DDIs in two of the studies included in the present review (53,55). Pharmacogenomics will become increasingly important as more factors are mapped and studied (58).

While the exact incidence of clinically significant DDIs is not established, clinicians have no doubt about the existence of DDIs as a clinically important entity. For lack of other information, clinicians must use their general knowledge about effects of different drug classes both to avoid and to suspect the presence of a DDI. Examples are to avoid, if possible, two drugs with anti-serotonergic action, and to carefully titrate a new drug with sedative effects in patients using an opioid. Moreover, an indisputable method to reduce the risk for DDIs is to reduce the number of medications. The literature shows that many patients with advanced disease receive unnecessary and/or futile drug treatments that either are unlikely to benefit them, or entail a risk for adverse drug reactions that outweighs any beneficial effects. Drugs in these categories should be discontinued (3,6,9,59,60).

In conclusion, this study demonstrates that drugs used for symptom control in patients with advanced cancer may cause serious DDIs with other drugs used to relieve symptoms, drugs used for the treatment of concomitant diseases, as well as anticancer medications. However, the current evidence for risk of DDIs involving drugs used to relieve symptoms is very limited and gives no precise estimates of risk.

Still, physicians caring for patients with advanced cancer should cautiously plan drug treatments, limit polypharmacy, avoid drug combinations which theoretically have a high risk of DDIs, and closely monitor patients for adverse drug reactions.

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INTRODUCTION

Most patients with advanced malignant disease take drugs to control symptoms. The number and role of drugs used for symptom control usually increase when the patients approach the last days of life (1,2). Additionally, many patients use drugs to treat concomitant diseases, and some continue anticancer medications (3,4). The total number of drugs taken regularly equals or exceeds five, the criterion of polypharmacy, in more than 80% of patients with advanced cancer, and one in four patients take ten or more drugs daily (criterion of hyperpolypharmacy) (3,5,6). This use of multiple medications raises the risk of serious adverse effects caused by drug-drug interactions (DDIs), which may be difficult to adequately diagnose and manage.

Multiple studies have demonstrated that patients with advanced cancer and other palliative care patients, including those in the last days of life, are exposed to a high number of potential DDIs (3,7–12). Published reports on clinically significant DDIs of opioids used for the treatment of pain in cancer patients have been summarized in a systematic review (13). However, clinical reports of significant DDIs of other classes of drugs used for symptom control in cancer patients, as well as of opioids used for the treatment of symptoms other than pain, have not been systematically reviewed.

The aim of the present review is to identify studies reporting clinically significant DDIs involving medications used for symptom control, other than opioids used for pain management, in adult patients with advanced malignant disease.

METHODS

Search strategy

Systematic searches were performed in Embase and MEDLINE through OvidSP, from set up of the databases (Embase from 1980) until June 2018. The last day searched was 21st June 2018. The full search strategy for Embase is presented in supplementary Table 1 (available online). Titles and abstracts of the retrieved citations were reviewed independently by two of the researchers (DFH, AKL), and potentially relevant papers were read in full text (DFH, AKL). In cases of doubt or dis-agreement, papers were reassessed by all three investigators (DFH, AKL, PK). Additionally, reference lists of all the papers read in full text were hand-searched for relevant papers.

A flow chart showing the selection of included papers is presented in Figure 1.

Figure 1. PRISMA flow chart showing the selection of papers

Inclusion criteria

– Publications reporting clinically significant DDIs involving drugs used for symptom control, excluding opioids used for pain management, in adult patients with advanced malignant disease, as assessed by the authors of the paper (irrespective of whether symptoms were related to cancer or comorbidities)

– Any type of publication: randomized controlled trial, other controlled study, observational study, case report, case series, or letter to the Editor, except for publications available only in abstract form

– Publications in English language

Exclusion criteria

– Experimental studies

– Only pharmacokinetic investigations (no clinical outcome)

Content analysis

The identified publications were grouped according to pharmacological class of drugs involved in the reported DDI, clinical manifestation, and proposed mechanism underlying the DDI. The DDIs and underlying mechanisms were presented according to the interpretations made by the authors of the individual papers. All of the DDIs were assessed using information in Lexicomp Drug Interaction Checker with respect to their severity, risk rating, and level of evidence (14).

RESULTS

Of 9699 retrieved citations, 462 were considered potentially eligible. After full-text reading, 29 were included in the final analysis, together with 13 papers identified through hand-searching of reference lists (Figure 1; Table 1) (15–56). Fifteen of the papers were published in the period 1978–2000, and 27 in the period 2001–June 2018. One of the case reports was supplemented by an erratum (Table 1) (57).

Of the 42 included publications, 30 were case reports presenting one or two relevant patients, 11 were letters to the Editor, and one was a retrospective study reporting four cases. No randomized controlled trials or other controlled studies were identified. In some publications, DDIs in both cancer patients and patients with non-malignant diseases were reported. From these publications, only cases of DDIs in patients with advanced malignant disease were included in the review. In total, the publications reported DDIs in 47 patients.

Of the identified DDIs, 24 (53.3 %) were of major severity, 10 (22.2 %) of moderate severity, and one (2.2%) of minor severity (14). Ten of the DDIs identified (22,2 %) Were not included in the Lexicomp drug-drug interactions database (Tabela 1).

Table 1. Overview of included publications

Drugs used for symptom control involved in DDIs, and clinical manifestations of DDIs

Drugs most often involved were antiepileptics (23 cases) (phenytoin in particular) and antidepressants (10 cases) (mostly selective serotonin reuptake inhibitors). Some DDIs were reported by more than one publication (16,17,20,22,23,25,26,33–35). Twenty publications related to DDIs of symptomatic drugs and oncologic agents (Table 1) (15–32,46,53). The details for all DDIs are given in Table 1.

Most cases of DDIs identified resulted from increased toxicity of the drug used to relieve symptoms or of co-administered drugs. In nine cases, DDIs led to failure of treatment, e.g. the recurrence of seizures in patients treated with an antiepileptic agent.

DDIs involving medications used for symptomatic treatment caused many different clinical manifestations: sedation and coma (20–27,33,40,41,53–55), ataxia (19–25,38,39), serotonin syndrome (42–45,47,49), seizures (28–32,34), liver and kidney failure (15–17,52), respiratory depression/failure (40,41,53–55), delirium (20,23,24,33,39), bleeding (36,56), visual impairment (23,38), cardiac arrhythmias

(48), neuroleptic malignant syndrome (51), rhabdomyolysis (46,50) and others (18,20,26,27,35–38).

Mechanisms underlying DDIs of drugs used for symptom control

Thirty publications identified pharmacokinetic DDIs and eight publications presented pharmacodynamic DDIs. Five publications reported a combination of both pharmacokinetic and pharmacodynamic DDIs (Table 1).

The most common mechanisms eliciting pharmacokinetic DDIs were alteration of drug metabolism (29 studies), including thirteen publications related to inhibition or induction of CYP2C9, CYP3A4 or CYP2C19 izoenzymes of cytochrome P450, and two studies related to glucuronidation. The other mechanisms of pharmacokinetic DDIs were proposed to be secondary to impaired absorption of drugs from the gastrointestinal tract, increased volume of distribution, displacement from protein binding sites, or decreased renal elimination.

Pharmacodynamic DDIs were caused by overstimulation of serotonin receptors in the CNS (five studies), inhibition of prostaglandin synthesis (three studies), as well as other and less clear mechanisms. In some publications, more than one mechanism underlying pharmacokinetic or pharmacodynamic DDIs was proposed (Table 1).

DDIs of non-opioid analgesics

The present review identified only four publications demonstrating DDIs of non-opioid analgesics (15–18). Three publications reported DDIs from combined use of a non-steroidal anti-inflammatory drug and methotrexate or cyclophosphamide. Three

patients using indomethacin experienced methotrexate toxicity manifested as renal failure (16,17), and one patient had a possible DDI of indomethacin and cyclophosphamide that resulted in water intoxication and severe hyponatremia (18). One case report presented a patient with fatal liver toxicity that resulted from concurrent use of acetaminophen, levothyroxine, and sunitinib (15).

DDIs of antiepileptics

Twenty-two publications in the present review concerned antiepileptic drugs (19–40). Eighteen of them referred to phenytoin, and five to other antiepileptic drugs: carbamazepine, valproic acid, and lamotrigine (Table 1). Nine studies reported phenytoin toxicity associated with elevation of its serum concentration above therapeutic range, which manifested as drowsiness, weakness and unsteady gait/ ataxia among other symptoms (19–27). One case reported thrombocytopenia proposed to be secondary to an interaction involving phenytoin, dexamethasone, and cimetidine (35).

In contrast, six cases reported seizures associated with sub-therapeutic serum levels of phenytoin (28–32,34). Three publications presented patients with brain tumors in whom the co-administration of phenytoin and dexamethasone produced diminished efficacy of the treatment, resulting in worsening of the patients' condition, and seizures (32–34). One case report referred to a patient in whom co-administration of warfarin and phenytoin resulted in anticoagulation failure (36).

The remaining reports on DDIs associated with the use of antiepileptics were publications reporting single cases of fatal toxic epidermal necrolysis caused by

combined use of lamotrigine and valproate sodium, carbamazepine toxicity secondary to concurrent use with propoxyphene or terfenadine, and methadone-induced respiratory depression after carbamazepine discontinuation (37–40).

DDIs of antidepressants

Ten publications in the present review reported DDIs of antidepressant medications: citalopram/escitalopram (five studies), sertraline, paroxetine, duloxetine, amitriptyline, trazodone, and nefazodone (one study each) (41–50). Six of these studies reported DDIs resulting in serotonin toxicity in patients with the antidepressant co-administered with medications modifying serotonergic activity in the CNS (opioids, linezolid), or inhibiting the metabolism of citalopram (fluconazole) (42–45,47,49). Two publications presented DDIs of antidepressant drugs manifested as rhabdomyolysis (46,50). One of these cases was believed to be a consequence of co-administration of the SSRI citalopram and irinotecan, two drugs competing for CYP3A4- mediated metabolism. Another case report presented rhabdomyolysis as a consequence of inhibition of simvastatin metabolism secondary to nefazodone, a strong CYP3A4 inhibitor. One publication reported a DDI manifested as opioid overdose in a patient in whom amitriptyline was co-administered with morphine (41). Sertraline combined with midazolam and fentanyl, three substrates of CYP3A4, were also associated with a DDI involving methadone, which led to torsades de pointes (48).

DDIs of antipsychotics

Only two cases of DDIs involving haloperidol were identified in the present review (51,52). One of these publications reported a case of neuroleptic malignant syndrome in a patient who was given haloperidol and fentanyl. Another report presented a possible pharmacokinetic DDI of voriconazole and haloperidol that

resulted in hepatotoxicity in a slow metabolizer of CYP2C19, the major isoenzyme responsible for voriconazole metabolism.

DDIs of corticosteroids

Five of the included publications referred to dexamethasone use (32–36). Four cases related to the concurrent use of the corticosteroid and phenytoin are described above. Two other cases presented pharmacodynamic DDIs of dexamethasone and captopril and acetylsalicylic acid, respectively, which resulted in arterial hypertension and bleeding from gastric ulceration (36).

DDIs of other medications used for symptomatic treatment

We identified seven publications that reported DDIs of other drugs used for symptomatic treatment, including an opioid overdose caused by codeine used for cough concurrently with clarithromycin and voriconazole (54), opioid overdose caused by concurrent use of methadone and cimetidine (55), altered mental status and respiratory failure caused by coadministration of diazepam and idelalisib (53), and two cases of bleeding reported to be secondary to the combined administration of drugs used for symptom control and anticoagulants (omeprazole and warfarin, and loperamide and dabigatran) (36,56). Two cases of DDIs with the possible contribution of cimetidine and midazolam are mentioned above (35,48).

Quality of evidence

The included studies have several limitations. Only case reports, letters to the Editor, and one retrospective study was identified (Table 1). Most of the reports included in this review provided poor level of evidence as judged by Lexicomp Drug Interaction

Checker (14) (28 DDIs (62.2 %) were assessed as having a fair level of evidence, six DDIs (13,3 %) good level of evidence, and only one (2.2 %) excellent evidence). Ten of the DDIs identified (22.2 %) were not included in the drug-drug interactions database (Table 1).

DISCUSSION

Drugs used for symptom control represent multiple classes of medications with variable and complex mechanisms of action and pharmacokinetics. Most of these drugs have potential for serious adverse effects and are known to interact with other medications. Patients with advanced malignant disease are prone to polypharmacy, frequent changes of co-administered drugs and doses, high incidence of organ failure, and numerous symptoms caused by the cancer. All these factors increase the risk for adverse effects due to DDIs. Still, this systematic review showed a limited number of reports of clinically significant DDIs in this patient population. Also, we were not able to find any systematic studies on the risk for such DDIs.

The most frequent drug classes involved were antiepileptics and antidepressants, and the most frequent DDI-related adverse effects were sedation, serotonergic syndrome and other neurologic complications/symptoms, and organ failure. As expected, some DDIs were related to pharmacokinetic interactions, and some to pharmacodynamic synergism or antagonism. Due to the lack of systematically obtained information, the literature can only point towards involved drug classes, symptoms and mechanisms, while no quantification of the importance of each of these factors is possible.

The present review demonstrates that evidence for DDIs of drugs used for symptom control in cancer patients (other than opioids used for pain treatment) is very limited. We identified only case reports, letters to the Editor and one retrospective study (Table 1). This result is consistent with our previously published review on DDIs of opioids used for pain treatment in patients with cancer (13). Seven of the publications included in the present review of drugs used for symptom control were also part of the opioid DDI review, because they concern interactions between opioids used for pain and another drugs used for symptom control. The unexpectedly low number of clinically significant DDIs of drugs used for symptom control is in contrast to the huge number of potential DDIs specified in drug interaction checkers recommended for use in populations of cancer patients and other palliative care patients (7,9–12).

The results of this review demonstrate that current knowledge gives no insight into the actual risk for DDIs in patients with advanced cancer. On the one hand, there is certainly an under-reporting of such incidences, while on the other hand, symptoms in patients using two or more drugs may be caused by other factors than a DDI, e.g. the disease itself, and erroneously be categorized as a DDI. The latter may be true for some of the proposed DDIs in this review, which seem to be less biologically plausible. Other study designs such as prospective observational studies consecutively including patients that have a specific new drug added to an established drug regimen, or including patients in whom one or more drugs are terminated when a certain adverse symptom is observed, are needed. However, even in such studies, it could be difficult to address if adverse effects be related to combining drug A and drug B, or stem from the drugs´ effects, regardless of their co-

administration. In fact, the ideal study would be to compare three groups; drug A alone, drug B alone, and drug A+B, in order to observe if there are any DDI effects. Studies on DDIs would also have to take into consideration genetic determinants affecting the studied interaction. Examples are variants causing poor and rapid CYP2D6 and CYP2C19 metabolizers, reported to cause the DDIs in two of the studies included in the present review (53,55). Pharmacogenomics will become increasingly important as more factors are mapped and studied (58).

While the exact incidence of clinically significant DDIs is not established, clinicians have no doubt about the existence of DDIs as a clinically important entity. For lack of other information, clinicians must use their general knowledge about effects of different drug classes both to avoid and to suspect the presence of a DDI. Examples are to avoid, if possible, two drugs with anti-serotonergic action, and to carefully titrate a new drug with sedative effects in patients using an opioid. Moreover, an indisputable method to reduce the risk for DDIs is to reduce the number of medications. The literature shows that many patients with advanced disease receive unnecessary and/or futile drug treatments that either are unlikely to benefit them, or entail a risk for adverse drug reactions that outweighs any beneficial effects. Drugs in these categories should be discontinued (3,6,9,59,60).

In conclusion, this study demonstrates that drugs used for symptom control in patients with advanced cancer may cause serious DDIs with other drugs used to relieve symptoms, drugs used for the treatment of concomitant diseases, as well as anticancer medications. However, the current evidence for risk of DDIs involving drugs used to relieve symptoms is very limited and gives no precise estimates of risk.

Still, physicians caring for patients with advanced cancer should cautiously plan drug treatments, limit polypharmacy, avoid drug combinations which theoretically have a high risk of DDIs, and closely monitor patients for adverse drug reactions.

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Figure 1. PRISMA flow chart showing the selection of papers
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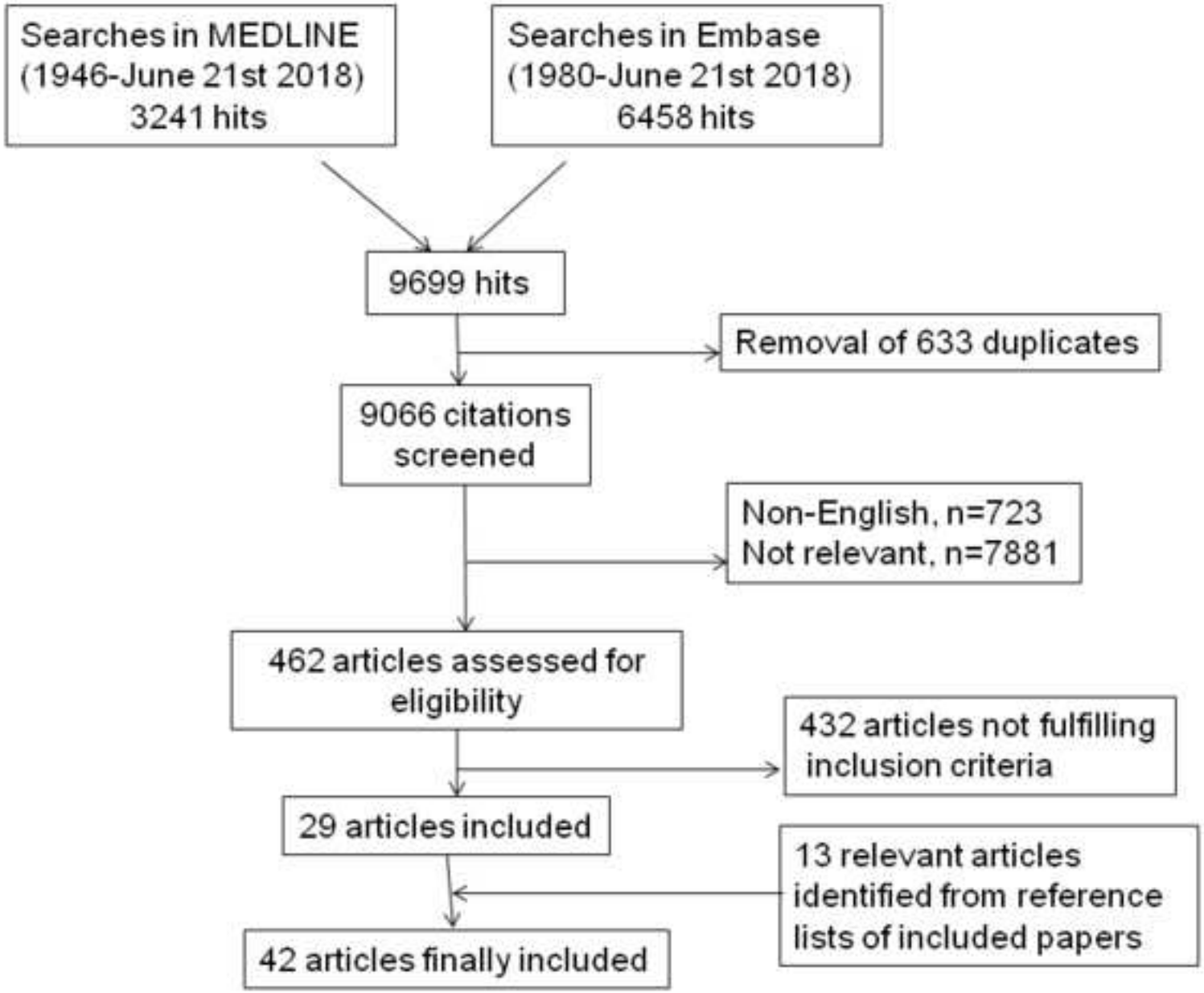

Table 1

Table 1. Overview of included publications

AUTHOR (YEAR) (Ref.) STUDY DESIGN	DRUGS CO-ADMINISTERED	CLINICAL PRESENTATION	Type of DDI	Underlying mechanism as proposed by the authors	LEXICOMP DRUG INTERACTION CHECKER ASSESSMENT		
					Severity	Reliability ratings	Risk rating
Weise et al. (2009) (15) Case report	Acetaminophen/levothyroxine/ sunitinib	Fatal liver failure	PD/ PK	Hepatotoxic effect of co-administered drugs, competition of acetaminophen and thyroxine for metabolic pathways,declining nutritional status after sunitinib reinitiation	ND	ND	ND
Maiche et al. (1986) (16) Letter to the Editor	Indomethacin/methotrexate	Renal failure	PD/ PK	Inhibition of renal PGs synthesis, decrease of renal MTX perfusion	Major	Good	D
Ellison and Servi (1984) (17)	Indomethacin/methotrexate (patient 1-2)	Fatal renal failure	PD/ PK	Inhibition of renal PGs synthesis, decreased	Major	Good	D

Case report				renal clearance of MTX			
Webberley and Murray (1989) (18) Case report	Indomethacin/ cyclophosphamide	Hyponatremia, water intoxication	PD	Toxic effect, inhibition of PGs, increased ADH activity	ND	ND	ND
Konishi et al. (2002) (19) Case report	Phenytoin/ doxifluridine (a prodrug of 5FU)	Phenytoin toxicity	PK	Inhibition of CYP2C enzymes	Major	Fair	D
Brickell et al. (2003) (20) Case report	Phenytoin/5FU/folinic acid (patient 1); phenytoin/capecitabine (patient 2)	Phenytoin toxicity	PK	Inhibition of CYP2C9	Major	Fair	D
Kuruvilla and Mukherjee (2011) (21) Letter to the Editor	Phenytoin/5FU	Phenytoin toxicity	PK	Inhibition of CYP2C9	Major	Fair	D
Privitera and de los Rios la Rosa (2011) (22) Case report	Phenytoin/capecitabine	Phenytoin toxicity	PK	Inhibition of CYP2C9	Major	Fair	D
Ciftci et al. (2015) (23) Case report	Phenytoin/capecitabine	Phenytoin toxicity	PK	Inhibition of CYP2C9	Major	Fair	D
Levy (2007) (24)	Phenytoin/temozolomid	Delirium; phenytoin	PK	Inhibition of CYP2C9	ND	ND	ND

Letter to the Editor		toxicity					
Grenader et al. (2007) (25) Case report	Phenytoin/erlotinib	Phenytoin toxicity	PK	Inhibition of CYP2C9, increase in unbound phenytoin	Major	Fair	D
Ohgami et al. (2016) (26) Case report	Phenytoin/erlotinib	Phenytoin toxicity	PK	Inhibition of metabolism or excretion of phenytoin	Major	Fair	X
Rabinowicz et al. (1995) (27) Case report	Phenytoin/tamoxifen	Phenytoin toxicity	PK	Competition for the enzyme system for metabolism	Major	Good	D
Neef and de Voogd-van der Straaten (1988) (28) Case report	Phenytoin, valproate sodium, carbamazepine/ cisplatin	Seizures	PK	Impaired absorption of carbamazepine and valproate sodium, increased metabolism or volume of distribution of phenytoin	ND	ND	ND
Dofferhoff and Berendsen (1990) (29) Letter to the Editor	Phenytoin/carboplatin	Seizures	PK	Displacement of phenytoin from protein binding sites and increased clearance	Moderate	Fair	C

Bollini et al. (1983) (30) Case report	Phenytoin/vinblastin and methotrexate	Seizures	PK	Impairment of phenytoin absorption	Major	Fair	D
Veldhorst-Janssen et al. (2004) (31) Letter to the Editor	Phenytoin/folinic acid (tegafur/uracil/calcium folinate therapy)	Seizures	PK	Increased phenytoin metabolism	Moderate	Fair	C
Gattis and May (1996) (32) Case report	Phenytoin/dexamethasone, cisplatin, dacarbazine	Seizures	PK	Impaired absorption and increased phenytoin metabolism	Moderate	Fair	C
McLelland and Jack (1978) (33) Letter to the Editor	Phenytoin/dexamethasone	Decreased dexamethasone efficacy	PK	Increased dexamethasone metabolism	Major	Fair	D
Recuenco et al. (1995) (34) Letter to the Editor	Phenytoin/dexamethasone	Decreased phenytoin and dexamethasone efficacy	PK	Increased metabolism of phenytoin and dexamethasone, displacement of phenytoin from binding sites	Major	Fair	D
Arbiser et al. (1993) (35) Case report	Phenytoin/dexamethasone, cimetidine	Thrombocytopenia	PD/ PK	Thrombocytopenic action of cimetidine and phenytoin intermediates,	Major	Fair	D

				interference with CYP3A4-mediated metabolism, increased levels of phenytoin epoxides			
Miranda et al. (2011) (36) Retrospective study	Phenytoin/warfarin	Deep venous thrombosis	PK	Increased warfarin metabolism	Major	Fair	D
Page et al. (1998) (37) Case report	Valproic acid/lamotrigine	Fatal toxic epidermal necrolysis	PK	Inhibition of lamotrigine glucuronidation	Major	Excellent	D
Oles et al. (1989) (38) Case report	Carbamazepine/propoxyphene	Carbamazepine toxicity	PK	Inhibition of CYP450-mediated metabolism	ND	ND	ND
Hirschfeld and Jarosinski (1993) (39) Letter to the Editor	Carbamazepine/terfenadine	Confusion, hallucinations, nausea and ataxia	PK	Displacement of carbamazepine from protein binding	ND	ND	ND
Benìtez-Rosario and Gómez-Ontañón (2006) (40) Letter to the Editor	Carbamazepine(discontinued)/ methadone	Coma and respiratory depression	PK	Disappearance of carbamazepine inducer effect on CYP3A4	Moderate	Fair	C
Upadhyay et al. (2008)	Amitriptyline/morphine	Coma and	PD/	Sedative effect, delayed	Major	Fair	D

(41) Case report		respiratory depression	PK	morphine metabolism			
Rang et al. (2008) (42) Case report	Paroxetine/fentanyl	Serotonin syndrome	PD	Hyperstimulation of serotonin receptors	Major	Fair	C
Walter et al. (2012) (43) Case report	Citalopram/oxycodone	Serotonin syndrome	PD	Hyperstimulation of serotonin receptors	Major	Fair	C
Bergeron et al. (2005) (44) Case report	Citalopram, trazodone/linezolid	Serotonin syndrome	PD	Hyperstimulation of serotonin receptors	Major	Fair	D
Levin et al. (2008) (45) Case report	Citalopram/fluconazole	Serotonin syndrome	PK	Inhibition of CYP2C19 and CYP3A4	Moderate	Fair	D
Richards et al. (2003) (46) Case report	Citalopram/irinotecan	Rhabdomyolysis	PK	Inhibition of CYP3A4	ND	ND	ND
Kirschner and Donovan (2010) (47) Case report	Escitalopram/fentanyl	Serotonin syndrome	PD	Hyperstimulation of serotonin receptors	Major	Fair	C
Walker et al. (2003) (48) Case report	Sertraline, midazolam, fentanyl/methadone	Torsades de pointes	PK	Interference with methadone metabolism	Moderate	Fair	C

Strouse et al. (2006) (49) Letter to the Editor	Duloxetine/linezolid	Serotonin syndrome	PD	Hyperstimulation of serotonin receptors	Major	Fair	D
Karnik and Maldonado (2005) (50) Case report	Nefazodone/simvastatin	Rhabdomyolysis	PK	Inhibition of CYP3A4	Major	Good	X
Morita et al. (2004) (51) Case report	Haloperidol/fentanyl	Neuroleptic malignant syndrome	PD	Antagonism at dopamine receptors, modification of dopamine metabolism (fentanyl)	ND	ND	ND
Motta et al. (2015, 2016) (52,57) Case report	Haloperidol/voriconazole	Hepatotoxicity	PK	Inhibition of CYP3A4 (patient CYP2C19 poor metabolizer)	Moderate	Fair	D
Bossaer and Chakraborty (2017) (53) Case report	Diazepam/idelalisib	Altered mental status (lethargic), respiratory failure	PK	Inhibition of CYP3A4	Major	Fair	X
Miranda et al. (2011) (36) Retrospective study	Dexamethasone/captopril	Arterial hypertension	PD	Sodium retention	ND	ND	ND
Miranda et al. (2011) (36) Retrospective study	Dexamethasone/acetylsalicylic acid	A gastric bleeding ulcer	PD	Overlapping toxicities to GI system	Moderate	Good	C

Gasche et al. (2004) (54) Case report	Codeine/clarithromycin and voriconazole	Coma and respiratory depression	PK	Inhibition of CYP3A4 (patient CYP2D6 poor metabolizer)	Moderate	Fair	C
Sorkin and Ogawa (1983) (55) Case report	Cimetidine/methadone	Coma and respiratory depression	PK	Inhibition of methadone metabolism	Minor	Fair	B
Miranda et al. (2011) (36) Retrospective study	Omeprazole/warfarin	Upper digestive hemorrhage	PK	Inhibition of hepatic metabolism of warfarin	Moderate	Good	C
Stöllberger et al. (2012) (56) Letter to the Editor	Loperamide/dabigatran	Gross hematuria	PK	Increased enteral absorption of dabigatran	ND	ND	ND

Abbreviations: DDI, drug-drug interaction; NSAIDs, nonsteroidal anti-inflammatory drugs; 5FU, 5-fluoruracil; MTX, methotrexate; CNS, central nervous system; GI, gastrointestinal; PD, pharmacodynamic; PK, pharmacokinetic; CYP2C9, CYP2C19, CYP2D6, CYP3A4, cytochrome P450 izoenzymes 2C9, 2C19, 2D6, 3A4 (respectively); PGs, prostaglandins; ADH, antidiuretic hormone; Ref., reference; Risk ratings: B: No action needed; C, Monitor therapy; D, Consider therapy modification; X, Avoid combination, ND, no data

Supplementary Table 1. Search strategy

Search strategy in Embase for drug-drug interactions (DDIs) involving drugs used for symptom control in patients with advanced malignant disease

#1 and (#3 or (#2 and #4))

#1 exp neoplasm and Human/ not (Animal experiment/ or Animal model/ or Animal tissue/ or exp Cell culture/ or Cell line/ or exp Tumor cell line/ or Exp In vitro study/ or Nonhuman/ or Tumor model/ or Human cell/ or exp Tumor cell/)

#2 drug interaction/ or drug antagonism/ or drug competition/ or drug inhibition/ or drug potentiation/ or polypharmacy/

#3 D*/it**

#4 D*

***D** denotes drug**,** with separate searches for the following drugs or drug classes:

1. paracetamol/acetaminophen > Paracetamol/
2. non steroidal antiinflammatory drugs/NSAIDs > exp Nonsteroid antiinflammatory agent/
3. metamizole > Dipyrone/
4. dextromethorphan/

5. opioids/narcotics >
6. narcotic antagonist > exp Narcotic antagonist/
7. antidepressants > exp Antidepressive agent/
8. selective serotonin reuptake inhibitor/SSRI > exp Serotonin uptake inhibitor/
9. antipsychotics > exp Neuroleptic agent/
10. phenothiazines > exp Phenothiazine derivative/
11. 5HT3 antagonists/ serotonin receptor antagonists > exp Serotonin 3 antagonist/
12. metoclopramide/
13. cisaprid
14. hyoscine/
15. H2-blockers > exp Histamine H2 receptor antagonist/
16. proton pump inhibitors > exp Proton pump inhibitor/
17. corticosteroids/ steroids > exp Corticosteroid
18. megestrol acetate/
19. laxative > exp Laxative/
20. loperamide/
21. muscle relaxants > exp Muscle relaxing agent/
22. benzodiazepines > exp Benzodiazepine derivative/
23. antiepileptics/anticonvulsants > exp Anticonvulsive agent/
24. somatostatin/

**it=emtree term linked to qualifier ‘drug interaction’

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