Pharmacist-led intervention on the inappropriate use of stress ulcer prophylaxis pharmacotherapy in intensive care units: A systematic review

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ABSTRACT

Purpose To determine the effectiveness of pharmacist-led interventions on the inappropriate use of SUP pharmacotherapy in ICUs.

Methods A systematic review was performed for relevant studies using searched PubMed, EMBASE (Ovid), the Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), and four Chinese databases including Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure (CNKI), and VIP from the establishment of databases to 12 March 2020. We conducted a descriptive analysis of participants, the intervention content and delivery, and the effects on inappropriate medication rates.

Results

From 529 records, 8 studies from 9 articles were included in the narrative synthesis. All studies were cohort studies, and the NOS quality stars ranged between 5 and 7. Only 1 (12.5%) cohort study was regarded as high quality. The time of appropriateness judgment and the criteria of 'appropriate' varied from included studies. Pharmacist interventions mainly included clarifying indications for SUP pharmacotherapy, education and awareness campaign, reviewed patients on SUP pharmacotherapy during rounds, and adjustments of drug use. Five (62.5%) studies found a significant intervention effect during hospitalization, while 2 (25%) studies at ICU transfer and 2 (25%) studies at hospital discharge. Four (50%) studies identified the complications related to SUP pharmacotherapy and found no significant difference. Four (50%) studies declared the pharmacist-led interventions were associated with cost savings.

Conclusion

Pharmacist-led interventions may be associated with a decrease in inappropriate SUP pharmacotherapy rates during hospitalization, at ICU transfer and hospital discharged. Further research is needed to determine whether the latest guidelines are more suitable for the management of SUP pharmacotherapy and whether pharmacist-led intervention is cost-effective.

Keywords Pharmacist-led; stress ulcer prophylaxis; intensive care unit; systematic review; quality improvement

INTRODUCTION

With the advancement of pharmacy directed patient care, the role of pharmacists has expanded from the traditional task of distributing medications and providing basic drug information to a team-based clinical role providing patient-centered medication therapy management.[1] Many studies have confirmed that pharmacists' direct intervention or participation in multidisciplinary management teams can improve the clinical outcome and quality of life of patients by optimizing the use of drugs in different disease processes.[2-9]

As a member of a multidisciplinary management team, pharmacists make full use of their professional knowledge and clinical experience to perform an important role in the care of intensive care unit (ICU) patients.[10] A previous systematic review sufficiently dissected the impact on patient outcomes of pharmacist participation in multidisciplinary critical care teams.[11] This paper clarified pharmacists' participation improved patient outcomes including mortality, ICU length of stay in mixed ICUs, and preventable/nonpreventable adverse drug events.[11]

Stress-related gastrointestinal bleeding (GIB) is common in critically ill patients and has been associated with an increased risk of death and ICU length of stay.[12] Preventing potential progression from stress related mucosal damage to GI bleeding, acid suppression therapies (AST) are often overused for stress ulcer prophylaxis (SUP). [13-17]

Although several studies had examined the impact of pharmacist-led de-escalating SUP pharmacotherapy, they had not been reviewed. Our systematic review aimed to determine the effectiveness of pharmacist-led interventions on the inappropriate use of SUP pharmacotherapy in ICUs.

METHODS

This systematic review conformed to the PRISMA statement and Synthesis without meta-analysis (SWiM) reporting guideline and was registered on PROSPERO (CRD42021239821).[18, 19]

Eligibility Criteria

We included studies evaluating the impact of pharmacist-led interventions on the use of stress ulcer prophylaxis in patients or in the intensive care unit. We included randomized controlled trials (RCTs), cohort studies, and case-control studies. There were no restrictions on language and publication time.

Search and Information Sources

We searched PubMed, EMBASE (Ovid), the Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), and four Chinese databases including Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure (CNKI), and VIP from the establishment of databases to 12 March 2020. We obtained additional articles by hand-searching reference lists of systematic reviews and other articles and from peer-reviewers.

Our search strategy used database-specific vocabulary (e.g., Medical Subject Headings) and free-text terms text expanding from 'stress ulcer prophylaxis', 'pharmacist', and 'critically ill'. For 'stress ulcer prophylaxis', in addition to the original deformed vocabulary, we searched clinical symptoms (such as gastrointestinal bleeding and gastric mucosal lesion) and specific preventive drugs (including H-2 receptor antagonist, proton pump inhibitors, and sucralfate).

The search strategy was developed specifically for each database (Appendix Table 1).

Study Selection

We used EndNote (version X8) reference manager for records management and duplicates

removal. Two investigators (WCT and XPP) screened all titles and abstracts. Once relevant articles were screened in, two investigators (WCT and XPP) independently screened full-text articles. All inconsistent inclusion decisions were resolved through consensus with a third reviewer (YQS).

Inclusion criteria followed the Participant-Intervention-Comparison-Outcome-Study Design (PICOS) framework.[20] Participants were patients in intensive care units who were critically ill or a short stay for observation. We excluded studies that focused on all departments but did not separately provide data from ICU departments. The intervention content could be provided in part or whole by the pharmacist (i.e., the pharmacist-led). The interprofessional approaches were included only when pharmacists participated in collaborative care interventions but only as assistants. We included studies of any design with a comparator group of usual care or other healthcare's intervention. We included studies with the incidence pharmacotherapeutic intervention in SUP as a primary or secondary outcome. We did not limit the observation time of outcome indicators, whenever during hospitalization, at ICU discharge, or hospital discharge.

Data Collection and Quality Assessment

Study data were extracted by one investigator (WCT) using specifically developed data extraction forms and checked by another investigator (XPP). Extracted data contained: (1) authors' name, year, the country of study origin and study purpose; (2) method (study design and information of study quality according to quality assessment criteria of different types of studies); (3) participant and setting (sample size, age, inclusion and exclusion criteria, indications for the use and cessation of SUP pharmacotherapy, the definition of rational use, and setting); (4) intervention (composition, implementer, and formation method); (5) outcomes (the incidence of the inappropriate use of SUP pharmacotherapy, cost of medications used for SUP, and complications of SUP pharmacotherapy; and (6) confirmation of eligibility for review.

We used the Cochrane risk of bias tool for assessing the risk of bias of RCTs and the Newcastle-Ottawa Scale for case-control and cohort studies.[21, 22]

Data synthesis and analysis

The primary outcome was the incidence of inappropriate use of SUP pharmacotherapy. Secondary outcomes included complications related to SUP pharmacotherapy and economic outcomes.

As the heterogeneity of the research inclusion criteria, the denominator was inconsistent when calculating the inappropriate rate. Therefore, we recalculated the rate using the SUP pharmacotherapy population during ICU hospitalization as the denominator to get the standardized metric. We excluded patients with chronic AST prior to admission if there was no reconsideration of the appropriateness of chronic AST.

Due to the expected heterogeneity of participants, interventions, and the definition of inappropriate, it was hard to group studies for synthesis and undertake a meta-analysis. We conducted a descriptive analysis of participants, the intervention content and delivery, and the effects on inappropriate medication rates.

Chi-square tests were used for categorical group comparisons based on pre- and post-intervention groups. Data were analyzed using IBM SPSS Statistics for Windows v22.0(IBMCorp., Armonk, NY). P-values<0.05 were considered statistically significant. For economic outcomes, we unified the monetary unit to the U.S. dollar (1 Australischer Dollar =0.778 US Dollar; 1 Canadian dollar =0.7891 US Dollar).

RESULTS

Study selection

A total of 529 studies were retrieved from the databases. From the total, 478 studies were excluded based on titles and abstracts and 12 studies were excluded based on full-text articles (Figure 1). Primary reasons for exclusion were non-ICU, non-pharmacist-led intervention, non-SUP-related medications, cannot extract ICU data separately, reviews, case reports, and duplicate literature (Figure 1). We included 8 studies from 9 articles in the narrative synthesis.[14, 23-30] All studies were cohort studies, of which 6 (75.0%) were retrospective and the other 2 (25.0%) were prospective. Observation periods ranged from 2 weeks to 6 months. All studies assessed appropriateness during ICU hospitalization. In addition, 4 (50.0%) studies assessed appropriateness at ICU transfer and hospital discharge at the same time (Table 1).

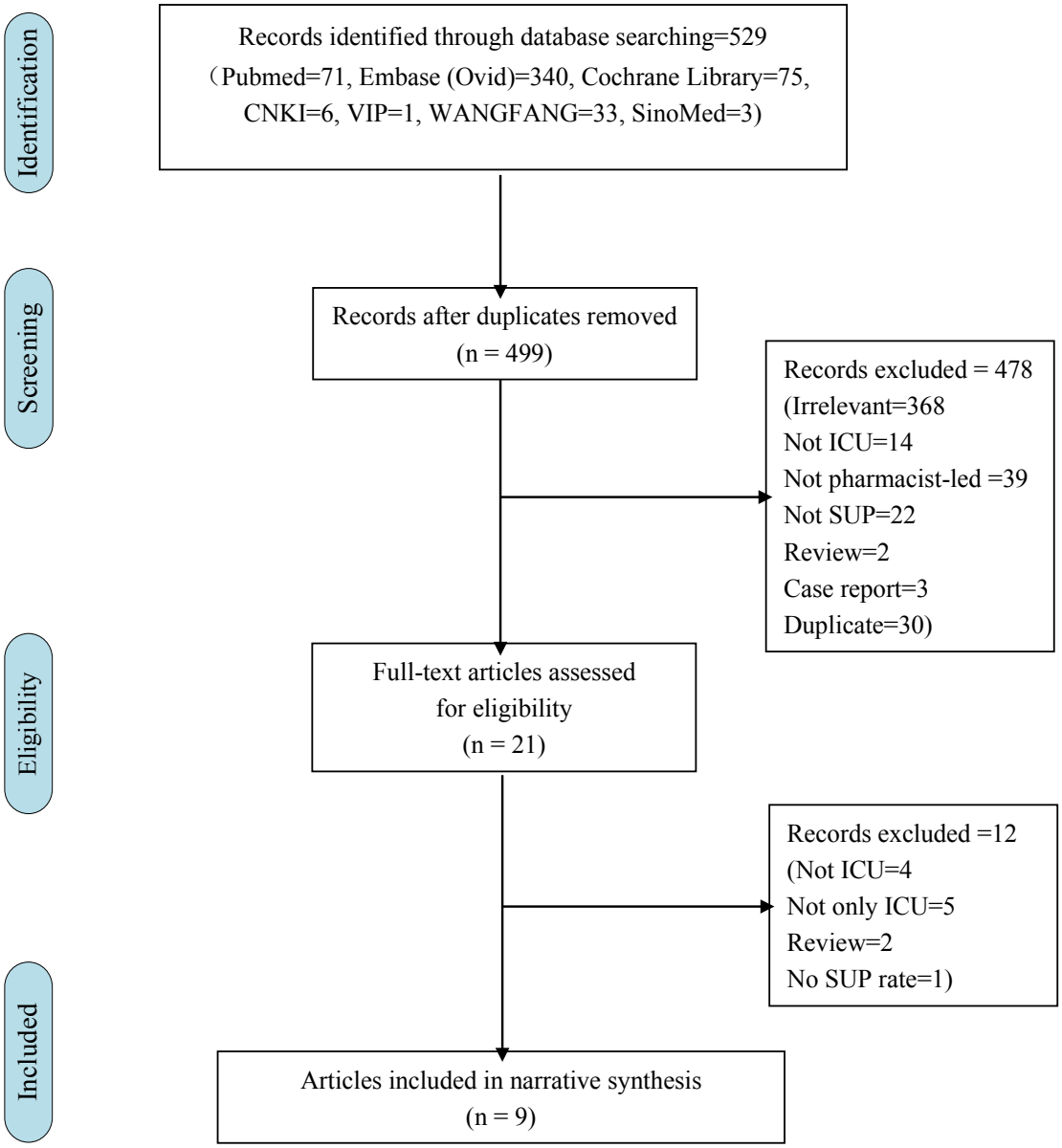

Figure 1. Flow chart for screened articles.

Table 1. Characteristics of included studies.

Study ID	Country	Study design	Center	Sample size		Observation periods (months)	Outcome measurement time point	Significant intervention effect? *
				Pre-	Post-			
Anstey 2019[23]	Australia	Prospective cohort study	5	531	393	5	ICU hospitalization Hospital discharge	No Yes
Masood 2018[24]	United States	Retrospective cohort study	1	162	202	1	ICU hospitalization	Yes
Hammond 2017[25]	United States	Retrospective cohort study	1	101	118	6	ICU hospitalization ICU transfer Hospital discharge	Yes No No
Buckley 2015[14]	United States	Retrospective cohort study	1	174	167	1	ICU hospitalization ICU transfer Hospital discharge	Yes Yes Yes
Fan 2015[26]	China	Retrospective cohort study	1	20	20	1	ICU hospitalization	No
Tasaka 2014[27]	United States	Retrospective cohort study	1	75	56	0.5	ICU hospitalization ICU transfer Hospital discharge	Yes No No
Wohlt, P. D. 2007[30] (pre-) Hatch 2010[28]	United States	Retrospective cohort study	1	494	458	1	ICU transfer Hospital discharge	Yes Yes
Coursol 2005[29]	Canada	Prospective cohort study	1	303	252	1	ICU hospitalization	Yes

Participant characteristics

Most studies included adult patients (6, 75.0%) and the other 2 (25.0%) did not specify the study population (Table 2). Regarding the type of ICU, two (25.0%) studies included patients in medical and surgical ICUs, two (25.0%) studies only included patients in medical ICU, and the other 4 (50.0%) studies did not specify the ICU category. Five (62.5%) studies included all patients admitted to the ICU, while 3 (37.5%) studies only focused on patients who received AST. Inclusion criteria varied between studies but most of them (5, 62.5%) excluded patients having an additional indication for AST (e.g., active GIB, active peptic ulcer disease, and Zöllinger-Ellison syndrome) or they were not indicated for SUP pharmacotherapy regardless of risk factors (e.g., total gastrectomy). [14, 25, 27-29]

Risk of bias within studies

The NOS quality stars ranged between 5 and 7, and the average score was 5.88 for cohort studies (Table 3). Only 1 (12.5%) cohort study was regarded as high quality (NOS ≥7 points).

Table 2. Participant characteristics of included studies.*

Study ID	Age (years)	Male sex	Department	Inclusion criteria	Exclusion criteria
Anstey 2019[23]	T: 59(40-71) C: 60(42-71) *	T: 230(58.5%) C: 301(56.7%)	ICU	·All adult (≥ 18 years) hospitalized patients	·Patients aged<18 years; ·Cases with missing AST data
Masood 2018[24]	NR	NR	Medical ICU	·All patients admitted to the ICU	·Patients had acute GI bleeding
Hammond 2017[25]	T: 56.24±18.35 C: 51.07±4.52	NR	Medical ICU	·All adult (≥ 18 years) hospitalized patients; ·Patients with an order for AST	·Patients possessed a current diagnosis of GIB; ·Patients on AST prior to admission to the ICU; ·Patients with a history of Zöllinger-Ellison syndrome
Buckley 2015[14]	T: 55.5±18.8 C: 58.3±17.1	T: 110(65.9%) C: 90(51.7%)	ICU	·All adult (≥ 18 years) hospitalized patients; ·Patients received either an H2RA or PPI	·Patients had GI diseases; ·Patients receiving AST prior to admission to the ICU
Fan 2015[26]	NR	NR	ICU	·All patients admitted to the ICU; ·Patients with an order for AST	-
Tasaka 2014[27]	≥18	NR	Medical and surgical ICU	·All adult (≥ 18 years) hospitalized patients	Patients had: ·Active GIB, ·Active peptic ulcer disease ·Total gastrectomy ·Solid organ transplant ·Dual antiplatelet therapy ·Concurrent antiplatelet and anticoagulation therapy ·Nonenteric coated pancrelipase via gastric feeding tube
Wohlt, P. D. 2007[30] **Hatch 2010**[28]	T: 55±19 C: 54±19	T: 269 (58.7%) C: 287 (58.1%)	Medical and surgical ICU	·All adult (≥ 18 years) hospitalized patients	Patients had a current diagnosis of gastrointestinal bleeding, Zöllinger-Ellison syndrome, prisoner status; ·Patients died while in the hospital
Coursol 2005[29]	18-90	T: 157 (62.3%) C: 191 (63.0%)	ICU	·All adult (≥ 18 years) hospitalized patients	·Patients refused treatment; ·Patients died <24 hours after admission; ·Patients who pregnant; ·Patients with gastrointestinal bleeding, or an active ulcer, or Zöllinger–Ellison syndrome

*T: post-intervention group; C: pre-intervention group.

Table 3. Risk of bias of included studies

		Anstey 2019[23]	Masood 2018[24]	Hammond 2017[25]	Buckley 2015[14]	Tasaka 2014[27]	Fan 2015[26]	Hatch 2010[28]	Wohlt, P. D. 2007[30]	Coursol 2005[29]
SELECTION	Representativeness of the Exposed Cohort	★	0	0	0	0	0		0	0
	Selection of the Non-Exposed Cohort	★	★	★	★	★	★		★	★
	Ascertainment of Exposure	0	0	0	0	0	0		0	0
	Demonstration That Outcome of Interest Was Not Present at Start of Study	★	★	★	★	★	★		★	★
COMPARABILITY	Comparability of Cohorts on the Basis of the Design or Analysis	★	0	★	★	0	★		★	★
OUTCOME	Assessment of Outcome	★	★	★	★	★	★		★	★
	Was Follow-Up Long Enough for Outcomes to Occur	★	★	★	★	★	★		★	★
	Adequacy of Follow Up of Cohorts	★	★	★	★	★	★		★	★
TOTAL		7	5	6	6	5	6		6	6

Intervention content and delivery

Pharmacist interventions mainly included 4 aspects: 1) clarify indications for SUP pharmacotherapy; 2) education and awareness campaign; 3) reviewed patients on SUP pharmacotherapy during rounds; 4) adjustments of drug use (Table 4).

Four (50%) studies clarified the indication for the initiation and discontinuation of SUP pharmacotherapy by developing locally SUP pharmacotherapy guidelines/protocol or algorithm.[14, 23, 27, 29] Four (50%) studies provided the medical staff with an educational intervention and/or supplied a pocket card of SUP pharmacotherapy indications for reference.[24, 25, 27, 28]

In 3 (37.5%) studies, pharmacists reviewed each patient on SUP pharmacotherapy during medical ICU rounds.[24, 25, 28] In 5 (62.5%) studies, pharmacists made appropriate changes on SUP pharmacotherapy, in which 2 (25.0%) studies gave the pharmacist prescriptive authority to make such changes (i.e. initiate, continue, discontinue, or modify the route of medication administration) for SUP pharmacotherapy only.[14, 23, 24, 27, 28]

Effects on inappropriate use of SUP pharmacotherapy

To clarify the definition of 'inappropriate', we first clarified the indication of SUP pharmacotherapy in all studies. Based on the most recent published guidelines and the latest evidence at the time of the study's initiation, the indications for and cessation of SUP pharmacotherapy were different in each study (Appendix Table 2,3). For the initiation of SUP pharmacotherapy, it involved 12 major risk factors (to meet one) and 14 minor risk factors (to meet two or more). The most common major risk factors were mechanical ventilation for >48 hours and coagulopathy which were used by 7 (87.5%) studies. The common minor risk factors were high-dose glucocorticoid use and severe sepsis or septic shock which were used by 5 (62.5%) studies and 4 (50.0%) studies. For the cessation of SUP pharmacotherapy, four (50.0%) studies specified that SUP pharmacotherapy should be ceased when there is no ongoing indication.[14, 23, 25, 27] Two (25.0%) studies specified that SUP pharmacotherapy should be ceased when patients are discharged from ICU.[24, 27] One (12.5%) study specified that SUP pharmacotherapy should be ceased when patients received enteral feeding.[23] Three (37.5%) studies did not specify the cessation of SUP pharmacotherapy.[26, 28, 29]

Between pre- and post- intervention groups, the assessment time of appropriateness varied from studies (Table 5). Seven studies comprised the incidence of inappropriate SUP initiation during ICU hospitalization, of which 5 (71.4%) studies found a significant intervention effect.[14, 24, 25, 27, 29] Four studies comprised the incidence of inappropriate continuation of SUP pharmacotherapy at ICU transfer, of which 2 (50.0%) studies found a significant intervention effect.[14, 28] Five studies included the incidence of inappropriate continuation of SUP pharmacotherapy at hospital discharge, of which 3 (60.0%) studies found a significant intervention effect.[14, 23, 28]

Effects on complications and economic outcomes

Four studies identified the complications related to SUP pharmacotherapy (Table 6). There was no significant difference in the incidence of *Clostridioides difficile*-associated disease, pneumonia or hospital-acquired pneumonia, gastrointestinal bleeding, and thrombocytopenia between pre- and post- intervention groups.

Four (50%) studies explored the economic benefits of pharmacist-led interventions improving SUP pharmacotherapy (Table 7). [14, 23, 24, 29] Anstey 2019 determined the extrapolated direct savings to all Australian intensive care units from reduced SUP pharmacotherapy were $1.61 million/year, and indirect savings from the reduction in complications were $12.86 million/year nationally.[23] Masood

2018 clarified the pharmacist-led interventions could reduce the cost of medications for inappropriate SUP pharmacotherapy during the study period from $2,433.00 to $239.80.[6] Buckley 2015 and Coursol 2005 identified the cost of the drugs for SUP per patient and clarified that the pharmacist-led intervention reduced it from $30.52±51.45 to $8.91±11.03 and $8.74 to $6.68.[9, 12]

Table 4. Intervention content and delivery of included studies

Study ID	Intervention						Design	Details	
	Indication		Education		Rounds	Adjustments of drug use		Content	Primary implementor
	local SUP guidelines/ protocol	Algorithm	Medical staff	Materials					
Anstey 2019[23]	●					●	NR	(a) A site-based dissemination of locally produced SUP prescription guidelines (b) ICU pharmacist-led discontinuation of SUP prior to ICU discharge	NR pharmacists
Masood 2018[24]			●	●	●	● (prescribe authority)	NR	(a) Pharmacists reviewed patients on SUP during medical ICU rounds (b) Pharmacists made appropriate changes (prescriptive authority) according to the guidelines. (c) Residents and fellows were educated and house staff were provided with printed copies of SUP indications.	pharmacists pharmacists pharmacists
Hammond 2017[25]			●	●	●		NR	(a) A pharmacist provided medical residents and pulmonary/critical care fellows with an educational intervention (b) Supplied a pocket card on SUP initiation and choice of agent (c) A pharmacist rounded with the medical ICU treatment team	pharmacists multidisciplinary team pharmacists
Buckley 2015[14]	●					● (prescribe authority)	NR	(a) An institutional SUP prescription protocol (b) Clinical pharmacists to initiate, modify, or discontinue stress ulcer	pharmacists pharmacists

							prophylaxis	
Fan 2015[26]						NR	NR	pharmacists
Tasaka 2014[27]	•		•		•	NR	(a) An institution SUP guideline (b) An education and awareness campaign (c) A pharmacist-led intervention	NR NR pharmacists
Hatch 2010[28]				•	•	NR	(a) A memorandum and a pocket card (b) Pharmacists also conducted medication reconciliation during daily patient care rounds and at discharge.	pharmacists pharmacists
Coursol 2005[29]		•				NR	Stress Ulcer Prophylaxis Algorithm	pharmacists
Amount	**4**		**4**	**3**	**5**			

Table 5. The rate of inappropriate use of SUP pharmacotherapy.

Study ID	**Rate of inappropriate use of SUP pharmacotherapy**								
	Initiation of SUP			**Continuation of SUP at ICU transfer**			**Continuation of SUP at hospital discharge**		
	pre-	**post-**	**P**	**pre-**	**post-**	**P**	**pre-**	**post-**	**P**
Anstey 2019[23]	19.81%	25.49%	0.198	-	-	-	36.79%	7.19%	＜0.001
Masood 2018[24]*△	26.75%	7.14%	＜0.001	-	-	-	-	-	-
Hammond 2017[25]	23.76%	12.71%	0.033	60.40%	53.39%	0.297	17.82%	13.56%	0.385
Buckley 2015[14]	14.38%*	6.03%*	＜0.001	67.82%	38.92%	＜0.001	29.89%	3.59%	＜0.001
Fan 2015[26]	0.00%	0.00%	-	-	-	-	-	-	-
Tasaka 2014[27]	21.26%*	9.09%*	0.004	8.00%	3.57%	0.498	6.67%	0.00%	0.131

Hatch 2010[28]	-	-	-	52.94%	27.27%	＜0.001	26.89%	15.74%	0.003
Coursol 2005[29]	95.74%	88.24%	0.033	-	-	-	-	-	-

*The rate was calculated based on patient-day.

△Only one study (Masood 2018) included inappropriate use of SUP on patients who changed oral chronic AST use into intravenous route.

Table 6. Complications related to SUP.

Study ID	Event	Pre-		Post-		P
		n	N	n	N	
Anstey 2019[23]*	*C. difficile*-associated disease	7	531	1	393	0.172
	C. difficile	0	101	0	118	-
Hammond 2017[25]	Pneumonia	5	101	6	118	0.964
	Stress-related mucosal bleeding	1	101	0	118	0.938
Buckley 2015[14]	Hospital-acquired pneumonia	29	174	25	167	0.668
	C. difficile-associated diarrhea	15	174	18	167	0.500
	Thrombocytopenia	11	174	5	167	0.146
	Gastrointestinal bleed	8	174	4	167	0.270
Coursol 2005[29]*	Significant bleeding	2	303	3	252	0.836

*The incident is based on all ICU populations, not just SUP populations.

Table 7. Economical outcomes related to SUP.

Study ID	Outcome	Pre-	Post-	Other
Anstey 2019[23]	Direct savings to all Australian intensive care units	-	-	$1.61 million/year
	Indirect savings from the reduction in complications to all Australian intensive care units	-	-	$12.86 million/year
Masood 2018[24]	Cost of drugs for inappropriate SUP during study period	$2,433.00	$239.80	-
Buckley 2015[14]	Cost of drugs for SUP per patient	$30.52±51.45	$8.91±11.03	-
Coursol 2005[29]	Cost of drugs for SUP per patient	$8.74	$6.68	-

DISCUSSION

Summary of evidence

This study was a systematic review of pharmacist-led interventions on the inappropriate use of SUP pharmacotherapy in intensive care units. Although the meta-analysis was not appliable for this review as the heterogeneous of judgment standards for the inappropriate use, we could speculate on the impact of pharmacist-led intervention through narrative synthesis. During hospitalization (7 related studies), the majority (71.4%, 5/7) indicated that pharmacist-led interventions were associated with a decrease in inappropriate SUP pharmacotherapy rates.[14, 24, 25, 27, 29] This ratio was 50% (4 related studies) at ICU transfer[14, 28] and 60% (5 related studies) at hospital discharged.[14, 23, 28] No studies (4 related studies) found an increased risk of complications related to SUP pharmacotherapy.[14, 23, 25, 29] All studies (100%, 4 related studies) indicated that pharmacist-led intervention was associated with significant costs-savings.[14, 23, 24, 29]

Pharmacist interventions varied among the identified studies and included several cointerventions. In general, for identified studies, the pharmacist-led interventions included clarifying indications for SUP pharmacotherapy, education and awareness campaign, review of patients on SUP during rounds and adjustments of drug use. A key role for health-system pharmacists is in the development and implementation of protocols, guidelines, and formularies for directing safe and effective use of medications that focus on patient safety and improved healthcare outcomes.[1] In the case of conflicting recommendations in the existing guidelines, only 4 identified studies (50%) had formulated the institution's protocol. Furthermore, even after the pharmacists' interventions, the rate of inappropriate use of SUP pharmacotherapy was still high at ICU transfer (3.57%-53.39%), which suggests that pharmacists in future studies and clinical practice should focus on the discontinuation of SUP pharmacotherapy. Targeting specific diseases, the pharmacists could stratify patients based on the risk of clinically important GIB and implement different interventions, rather than regarded critically ill patients as a broad target group.

One proposed benefit of pharmacist-led intervention for use of SUP pharmacotherapy is decreased medical expenses. Only 4 studies reported the economic benefits of pharmacist-led interventions improving SUP pharmacotherapy and there was no cost-effectiveness analysis. Further research is needed with economic impact and cost-effectiveness analysis of pharmacist-led intervention.

Only one study was deemed to be of high quality, and most of studies (87.5%) have selection bias, including representativeness of the exposed cohort (87.5%) and ascertainment of exposure (100%). All studies only described the content and deliverer of intervention, but no process outcome being reported, such as the number of a modification proposal was made and the number of suggestions adopted by physicians. In addition, no studies have considered the cost of pharmacist intervention, which is not conducive to stakeholders' decision-making. Since almost all studies were single-center with poorly representative of the community, the conclusions may not extrapolate to other institutions or country.

Strength and limitations

Compared with published reviews,[31, 32] we standardized the calculation process of the inappropriate rate so that the results of the studies were comparable. We also discussed the primary outcome at different time points including during ICU hospitalization, at ICU transfer and hospital discharge. In

addition, we fully discussed the heterogeneity between the studies, and have a more correct explanation of the synthesis of the evidence in this review.

Due to the heterogeneity of identified studies, not only the studies' results, but also the design of studies including the definition of 'inappropriate', the pharmacists' interventions, and the time of the judgment of appropriateness, it was difficult to precisely identify the impact of pharmacist-led interventions on the inappropriate use of SUP pharmacotherapy in intensive care units and which intervention was more efficient. We excluded several studies because of lacking key data. We were unable to contact the original author for more detailed information, which adds to the bias of this review. Besides, during the recalculation, the rate of inappropriate use of SUP pharmacotherapy at ICU transfer and hospital discharge may be underestimated as we used the SUP pharmacotherapy population during ICU hospitalization as the denominator.

Conclusions

Pharmacist-led intervention may be associated with a decrease in inappropriate use of SUP pharmacotherapy during hospitalization, at ICU transferred and hospital discharged. Further research is needed to determine whether the latest guidelines are more suitable for the management of SUP pharmacotherapy and whether pharmacist-led intervention is cost-effective.