Medication Safety in the Hospital Setting -

Role and Tools for the Swiss Hospital Pharmacist

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ABSTRACT

BACKGROUND

Following the Institute of Medicine's 1999 report "To Err is Human", patient safety has received increased attention with regulatory agencies and health care facilities. While a wide variety of initiatives have been started, today, more than 10 years after this landmark report, patient safety outcomes remain unchanged. Consequently, it is critical to develop new, effective approaches to improve medication safety in health care facilities. Major medication safety organizations recommend the use of multidisciplinary teams toward the identification and resolution of medication errors.

The role of Swiss hospital pharmacists has changed substantially over the last decade. In the past, the pharmacist's responsibility centered upon the timely dispensing and delivery of medication. However, at the present time, the hospital pharmacist is involved as a critical partner in the entire medication use process, focusing on the safe and effective use of drugs.

The aims of this work are to 1) Describe Swiss hospital pharmacists' perceptions of their current and future role in medication safety and 2) Identify efficient tools to allow hospital pharmacists to proactively address medication safety.

PROJECTS

Chapter 1: Survey of medication safety activities in Swiss hospitals: The role of the hospital pharmacist

A structured online survey was sent to all 41 Swiss hospital pharmacy directors to assess current medication safety activities and planned projects, specifically evaluating the role of the pharmacist. The 26 respondents (response rate 62%) employed an average of 0.76 pharmacist full-time employees per 100 beds (European average: 1 full-time employee per 100 beds). Swiss hospital pharmacists are participating in pharmacy & therapeutics committee meetings (23/26 hospitals, 88%) and providing pharmacovigilance (12/26, 46%). Clinical pharmacy services are offered in 25/26 institutions (96%) Other activities identified among 22 participants included the implementation of eHealth tools (11/22 hospitals, 50%) and the increase of clinical pharmacy services (4/22, 18%).

Tools most likely used in medication safety activities among 24 respondants were direct observation (23/24, 96%), critical incident reporting system (20/24, 83%), and chart review (16/23, 67%). Surveys (7/24, 29%) and analysis of MedWatch data (8/26, 33%) were less often utilized. Of the respondents, 38% (9/24) were not familiar with the trigger tool technology.

Chapter 2: Evidence-based reviews for the comparative evaluation of drug products

The American Society of Health-System Pharmacists (ASHP) considers an institutional multidisciplinary pharmacy & therapeutics committee and the appropriate management of the drug formulary as key steps toward safe medication therapy in the inpatient setting. An objective evaluation and formulary selection process is key for safe medication management. Potential templates for an evidence- based, efficient approach to drug evaluation are suggested.

Chapter 3: Medication safety assessment methods: How can institutions efficiently address drug-related problems?

Organizations, including the Institute for Safe Medication Practice, recommend different methods for the assessment of medication safety, including incident reporting (IR), direct observation (OB), chart review (CH) and trigger tool analysis (TR). However, the optimal method for identifying drug-related problems (DRPs) is unknown.

Pubmed, Embase and Scopus databases were systematically searched for any comparative study in which IR, OB, CH and TR were compared to one another. Twenty-eight studies were included in this review.

All four assessment techniques have different strengths and weaknesses. Overlap between different methods in identifying DRPs is minimal. While TR appears to be the most effective and labor-efficient method, IR best identifies high severity DRPs. Considering the lack of overlap and the ability of each method to identify different medication errors, the use of a combination of methodologies is strongly recommended.

Chapter 4: Medication use evaluation via manual trigger tool methodology in the inpatient setting

Once a product is added to the formulary, regular medication use evaluations are warranted. The trigger tool is an efficient and labor-efficient method for the assessment of medication safety. Consequently, a manual trigger tool form for the evaluation of intravenous heparin use was developed and piloted.

A systematic literature review (Pubmed, Embase, Scopus) identified 79 heparin-related safety indicators of which 19 were included into the manual trigger tool form.

The inclusion of only 20 randomly selected patients in a once-yearly assessment allowed the efficient identification of critical steps in the medication use process and subsequent continuous quality improvement projects.

Chapter 5: The FDA extended warning for intravenous haloperidol and torsades de pointes: How should institutions respond?

In September 2007 the Food and Drug Administration (FDA) strengthened label warnings for intravenous haloperidol regarding cardiac adverse events, including QT prolongation (QTP) and torsades de pointes (TdP), based on incident reporting.

Case reports were identified by searching the current literature (Pubmed, Embase, Scopus) as well as by analyzing the FDA's adverse event database.
Seventy cases of IV haloperidol-associated cardiac adverse events were identified; supporting that IV haloperidol can be associated with QTP and TdP. However, this complication most often took place in the setting of concomitant risk factors. Importantly, our results suggest that a total cumulative dose of IV haloperidol of < 2mg can safely be administered without electrocardiographic monitoring in patients without concomitant risk factors.

Chapter 6: The case of IV haloperidol – Does the WHO pharmacovigilance database offer evaluable comparative safety data?

In addition to the analysis of the FDA database, WHO adverse drug reaction (ADR) reports of QTP, TdP and/or cardiac arrest involving haloperidol, olanzapine and quetiapine, including different routes of administration, were analyzed and compared.
WHO and FDA pharmacovigilance data is based upon health care provider reported adverse drug events. However, considering that the total number of patients receiving the medication usage is unavailable, it is not possible for agencies to determine a true rate of incidence of an adverse drug event. Nonetheless, regulatory agencies, including the WHO and FDA, rely upon these reports to make recommendations regarding the safe, effective use of medications.
The case of IV haloperidol exemplifies the difficulties associated with reliance upon this database for regulatory decisions.The comparative trending analysis showed an overall higher number of cardiac ADR reports for oral haloperidol than for the IV administration. In addition, the number of overall cardiac ADRs involving QTP and/or TdP was greater for quetiapine or olanzapine compared to haloperidol. The reporting odds ratio, although of very limited use for comparative evaluation, revealed no significant difference in reporting for haloperidol and quetiapine. Due to the limited options for the treatment of acute psychotic events, a thorough risk/benefit evaluation for the choice of the appropriate drug is warranted until further controlled comparative studies are available.

CONCLUSION

Although staff resources are limited, our survey showed that Swiss hospital pharmacists are proactively participating in medication safety activities.
Several available methods allow for an effective, labor-efficient approach to medication safety assessment. With Swiss physicians increasingly dispensing drugs and the discipline of pharmacology also in the hands of physicians, comprehensive medication safety assessment potentially creates important professional opportunities for hospital pharmacists in Switzerland.

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GLOSSARY & DEFINITIONS

In the German speaking area of Europe, no standardized glossary for medication safety has been stipulated so far. In order to standardize the vocabulary and definitions of this work, a short overview of important terminology related to medication safety is presented in this chapter.

Begriff Englisch ***Abkürzung***	**Begriff Deutsch** ***Abkürzung***	**Erklärung**
Adverse drug event *ADE*	Unerwünschtes Arzneimittelereignis	Ein unerwünschtes Ereignis, verursacht durch das Medikament selber oder durch dessen fehlerhafte Verwendung.[2] Der Begriff „unerwünschte Arzneimittelwirkung“ umfasst sowohl Medikationsfehler wie auch unerwünschte Arzneimittelreaktionen.[5] Das unerwünschte Arzneimittelereignis ist das Ergebnis einer medikamentösen Behandlung, das zu einer verlängerten Behandlungsdauer führen kann und nicht dem zugrundeliegenden Gesundheitszustand des Patienten zuzuschreiben ist. Das Ereignis ist direkt auf die Anwendung oder Verabreichung eines Medikamentes zurückzuführen.[3;4]
Adverse drug reaction *ADR*	Unerwünschte Arzneimittelwirkung UAW	Eine durch das Arzneimittel selbst verursachte unerwünschte Wirkung.[2] Jede gesundheitsschädliche und unbeabsichtigte Wirkung eines Medikaments, die in Dosierungen auftritt, welche beim Menschen zur Prophylaxe, Diagnostik oder Therapie üblich sind.[3;4]
Adverse event *AE*	Unerwünschtes Ereignis	Ein nicht beabsichtigtes Vorkommnis im Zusammenhang mit einer medizinischen Behandlung, das zur Beeinträchtigung des Zustandes eines Patienten beiträgt oder beitragen könnte.[2;6] Eine Schädigung, die auf das medizinische Management und nicht auf die Erkrankung eines Patienten zurückzuführen ist. Ein unerwünschtes Ereignis kann das Ergebnis eines Fehlers sein. Ein unerwünschtes Ereignis hat eine Schädigung zur Folge, die das Ergebnis einer medizinischen Behandlung ist, zu einer verlängerten Behandlungsdauer führen kann und nicht dem zugrundeliegenden Gesundheitszustand des Patienten zuzuschreiben ist.[3;7] Vorkommnisse bzw. Ereignisse, die möglicherweise, aber nicht zwangsläufig zu einem konsekutiven Schaden für den Patienten führen.[1]
Adverse reaction	Unerwünschte Wirkung	Möglicher „Nebeneffekt“ einer medizinischen Intervention, oft auch billigend in Kauf genommen oder unvermeidbar.[1]
Causality	Kausalität	Der Arzt ist für einen durch einen vorwerfbaren Behandlungsfehler verursachten Schaden rechtlich verantwortlich. Notwendig für die Annahme einer haftungsbegründenden Kausalität ist, dass der (Primär-) Schaden mit praktischer Gewissheit auf dem Fehler beruht. Diese liegt vor, wenn eine überzeugende Wahrscheinlichkeit im Sinne persönlicher Gewissheit gegeben ist, welche Zweifeln Schweigen gebietet, ohne sie völlig auszuschließen.[1]
Compliance	Compliance	Konformität mit Instruktionen, insbesondere bezogen auf die Medikamenteneinnahme entsprechend den Anweisungen des Verschreibers.[2] Modernere Begriffe für „Compliance“ sind „Adhärenz“ (adherence) und Konkordanz (concordance).[2]

Begriff Englisch ***Abkürzung***	**Begriff Deutsch** ***Abkürzung***	**Erklärung**
Complication	Komplikation	Nicht geplanter und / oder unerwarteter Verlauf, der die Heilung erschwert, beeinträchtigt oder vereitelt; s. auch unerwünschtes Ereignis. Eine Komplikation kann auch auftreten als schicksalhafter Krankheitsverlauf, etwa bei Verschlimmerung einer Erkrankung oder als Folge einer diagnostischen oder therapeutischen Maßnahme.[1]
Concordance	Konkordanz	Zustimmung eines mündigen Patienten zu einer Therapie, basierend auf seinem Verständnis der therapeutischen Ziele, Verhandlungen, Akzeptanz und Commitment zur Therapie („informed consent").[2]
Critical incident Sentinel event	Kritisches Ereignis	Ein schwerwiegendes Ereignis, das zu einem unerwünschten Ereignis führen könnte oder dessen Wahrscheinlichkeit deutlich erhöht.[6] Ein Outcome oder ein anderes wichtiges unerwünschtes Ereignis, das in der Gegenwart adäquater Behandlung nicht auftritt.[2] Ein Ereignis, das mit einem Schädigungspotential einhergeht. Erfolgt keine Einleitung einer Gegenmassnahme, kann dieses kritische Ereignis zur Schädigung führen.[3;4]
Critical incident reporting system	CIRS	Zwischenfallerfassung ist die Meldung von kritischen Ereignissen oder Beinahe-Ereignissen. Je mehr Zwischenfälle erfasst werden, desto größer ist die Chance, Schwachstellen im System zu erkennen und durch geeignete Maßnahmen zu eliminieren. Werden Beinahefehler reduziert, entstehen weniger echte Fehler.[1]
Database	Datenbank	Eine strukturierte Sammlung von Daten, zur raschen Wiederfindung gedacht.[2]
Delphi process	Delphi Verfahren	Schriftliches, objektiviertes Evaluationsverfahren zur Erreichung eines fachlichen Konsens in einer Gruppe von Experten auf einem bestimmten Gebiet.[2]
Disease (v.s. illness = patient's perception)	Erkrankung / Krankheit	Eine Abnormalität oder Störung der körperlichen Struktur oder Physiologie; die professionelle Interpretation einer Erkrankung, basierend auf den Schilderungen einer Person (eines Patienten) in Kombination mit zusätzlichen Informationen von physischen Untersuchungen und Laboranalysen.[2]
Drug therapy problem Drug-related problem DRP	Medikations-assoziiertes Problem	Jegliche Umstände, die eine kompetente Fachperson als inkonsistent mit der Erreichung des therapeutischen Ziels beurteilen würde. Ein potentielles / theoretisches Medikations-assoziiertes Problem besteht in einer Diskrepanz zwischen dem tatsächlichen Behandlungsplan und den vorgegebenen Richtlinien. Ein tatsächliches Medikations-assoziiertes Problem erfordert ein Abweichen von einer Guideline in Kombination mit einer physischen Manifestation in Zusammenhang mit einem Symptom oder einem von der Norm abweichenden Laborwert.[2]
drug-related morbidity	Medikations-assoziierte Morbidität	Eine unerwünschte Patienten-Verletzung mit einem wissenschaftlich plausiblen kausalen Zusammenhang mit entweder a) einer Medikamententherapie und/oder b) einer unbehandelten Indikation für eine Medikamententherapie. Medikations-assoziierte Mortalität beinhaltet signifikante unerwünschte Arzneimittelwirkungen oder toxische Effekte, Therapieversagen, und Situationen mit einer unbehandelten Indikation.[2]

Begriff Englisch ***Abkürzung***	**Begriff Deutsch** ***Abkürzung***	**Erklärung**
Effectiveness	Wirksamkeit / Effektivität	Günstige Effekte eines Medikamentes unter nicht-idealen Bedingungen im täglichen klinischen Gebrauch.[2]
Efficacy	Wirksamkeit	Günstige Effekte eines Medikamentes unter idealen Bedingungen, z.B. eine kontrollierte klinische Studie.[2;6;8]
Efficiency	Wirksamkeit / Effizienz	Günstige Effekte eines Medikamentes beurteilt unter Berücksichtigung der benötigten Ressourcen.[2]
Error	Fehler	Eine Handlung oder ein Unterlassen bei dem eine Abweichung vom Plan, ein falscher Plan oder kein Plan vorliegt. Ob daraus ein Schaden entsteht, ist für die Definition eines Fehlers irrelevant.[2;6;8] Ein richtiges Vorhaben wird nicht wie geplant durchgeführt, oder dem Geschehen liegt ein falscher Plan zugrunde.[1]
Guideline	Richtlinie Leitlinie	Eine systematisch entwickelte Beschreibung von wünschenswerten Behandlungsentscheidungen unter spezifischen klinischen Umständen in einem typischen Patienten. Die Evidenz-basierte Leitlinie wird in der Regel durch einen formalen, konsultativen Prozess entwickelt und beinhaltet klinische Evidenz, Expertenmeinungen und professionelle Beurteilung. Eine Leitlinie kann auf Prävention, Diagnose oder Behandlung abzielen. Der Hauptzweck ist die Evidenz-basierte Behandlung der Patienten.[2] Leitlinien sind systematisch entwickelte Empfehlungen für Ärzte über die angemessene Vorgehensweise in Diagnostik und Therapie bei speziellen Erkrankungen zur Wahrung von Qualitätsstandards in der medizinischen Versorgung. Sie sind keine verbindlichen Rechtsnormen, sondern Orientierungshilfen im Sinne von „Handlungs- und Entscheidungskorridoren“, von denen im begründeten Einzelfall abgewichen werden kann oder muss.[1]
Incidence	Inzidenz	Die Anzahl neuer Fälle in einer Population pro Zeiteinheit. Ein Mass für die Frequenz für das Auftreten eines Ereignisses in einer Population, z.B. einer neuen Erkrankung. Der Nenner ist die Risikopopulation, der Zähler ist Anzahl auftretender Fälle während einer spezifischen Zeiteinheit.[2]
Incident	Zwischenfall	Ein Ereignis (Incident) im Rahmen einer Heilbehandlung, welches zu einer unbeabsichtigten und /oder unnötigen Schädigung einer Person oder zu einem Verlust hätte führen können oder geführt hat.[1]
Incident reporting system	Fehlermeldesystem	Relevante Fehler, die von Ärzten und anderen Leistungsträgern im Gesundheitswesen beobachtet oder begangen werden, können über strukturierte Datenerfassungssysteme gemeldet werden. Solche Meldesysteme, einschließlich Umfragen unter Leistungsträgern und strukturierte Befragungen, stellen eine Möglichkeit dar, die Leistungsträger im Gesundheitswesen an Forschungs- und Qualitätsverbesserungsprojekten zu beteiligen.[1]
Indicator	Indikator	Eine Beobachtung oder Messung, welche den zugrundeliegenden Zustand widerspiegelt. Ein als Indikator geeignetes Signal / Symptom ist stark korreliert mit dem eigentlichen Zustand / Ereignis, hoch signifikant und praktisch schlüssig.[2]

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Injury	Schaden	Ein Schaden liegt vor, wenn der negative Nutzen einer medizinischen Massnahme den positiven Nutzen übersteigt (Nettonutzenprinzip).[3] Eine schwerwiegender, gefährlicher oder beeinträchtigender klinischer Ausgang, der nicht korrigierbar ist oder signifikante zusätzliche Ressourcen zur Behandlung benötigt, wie z.B. eine Notfallbehandlung oder eine Hospitalisation.[2]
Latent error Systematic error	Systemfehler	In einem Arbeitssystem latent vorhandener Fehler oder fehlerhafter Prozess, der bei Zusammentreffen mehrerer Ereignisse oder Versagens mehrerer „Schutzfunktionen“ auftritt; oft fokussiert auf eine Person oder einen Vorgang.[1]
Medical error	Medizinischer Fehler	Ein „medizinischer Fehler“ (medical error) ist definiert als jede geplante Vorgehensweise, die nicht plangemäß ausgeführt wurde (d.h. Ausführungsfehler) oder das Anwenden einer Vorgehensweise, die zum Erreichen eines Ziels ungeeignet ist (Planungsfehler).[1]
Medication error	Medikationsfehler	Im angelsächsischen Sprachraum wird ein „Medikationsfehler“ definiert als eine Medikamentengabe, die anders als in der Krankenakte vermerkt, verabreicht wurde; Medikationsfehler gelten als Systemfehler. Es werden verschiedene Kategorien unterschieden: - nicht zugelassenes Medikament - zusätzliche Dosis - Dosierungsfehler - Unterlassung einer Verordnung - falscher Verabreichungsweg (z.B. oral statt intramuskulär) - ungeeignete Darreichungsform - falsche Verabreichungstechnik - falscher Verabreichungszeitpunkt.[1]
Mistake	Irrtum	Im englischen „Mistake“; eine geplante Vorgehensweise, die nicht plangemäß vollendet wird, bzw. Anwendung einer Vorgehensweise, die zum Erreichen eines gegebenen Ziels ungeeignet ist. Anders als im Bereich der deutschen Rechtsprechung wird in Untersuchungen und Berichten aus englischsprachigen Ländern der Begriff des Fehlers „error“ nicht notwendiger Weise im engen Kontext mit Vernachlässigung der Sorgfaltspflicht und Schaden gebraucht. Einem Behandlungsfehler mit vermeidbarem Schaden entspricht am ehesten der Terminus „negligence“ (Vernachlässigung), was in der Regel gleichbedeutend ist mit „substandard care“. Konsequenzen dieser uneinheitlichen Begriffsdefinitionen sind u.a. unterschiedliche Angaben zur Häufigkeit von unerwünschten Ereignissen, Fehlern und Schäden in der medizinischen Versorgung. In den meisten Publikationen zunächst definiert als Problem in der Versorgung, handelt es sich meist nur einen „Ergebnisparameter“ mit dem die Untersucher definieren wollen, ob ein unerwünschtes Ereignis als vermeidbar angesehen werden kann/konnte.[1]

Begriff Englisch ***Abkürzung***	**Begriff Deutsch** ***Abkürzung***	**Erklärung**
Near miss Potential adverse event	Beinahe-Ereignis Beinahe-Fehler	Ein Fehler ohne Schaden, der zu einem Schaden hätte führen können.[6] Ereignisse, bei denen ein Schaden trotz eines Fehlers ausgeblieben ist. Ereignisse, bei denen durch Korrektur eines Fehlers ein Schaden verhindert werden konnte, zählen ebenfalls zu den Beinahe-Schäden.[3;4] Fehler, wobei das Abweichverhalten rechtzeitig erkannt wird und so ein tatsächlicher Fehler vermieden wird. Als Beinahe-Fehler gilt jedes Vorkommnis, das unerwünschte Folgen hätte haben können, es im konkreten Fall jedoch nicht hatte und abgesehen vom Ergebnis (Outcome) von einem „richtigen“ (tatsächlich eingetretenen) unerwünschten Ereignis nicht zu unterscheiden war.[1]
Negative predictive value	Negativer prädiktiver Wert	Die Wahrscheinlichkeit, dass ein negatives Resultat tatsächlich negativ ist.[9]
Negligent adverse event	Unerwünschtes Ereignis durch Fahrlässigkeit	Ein Behandlungsfehler, wenn die ärztliche, pflegerische oder therapeutische Handlung gegen bewährte Handlungsregeln oder gesicherte medizinische Erkenntnisse verstösst.[3;4]
Patient safety	Patientensicherheit	Patientensicherheit ist das Produkt aller Maßnahmen in Klinik und Praxis, die darauf ausgerichtet sind, Patienten vor vermeidbaren Schäden in Zusammenhang mit der Heilbehandlung zu bewahren.[1] Im englischen Sprachraum versteht man unter „Patientensicherheit“ das Vermeiden, die Verhütung und Verbesserung von unerwünschten Ergebnissen oder Schäden durch Gesundheitsversorgungsmaßnahmen. Solche Ereignisse umfassen “Fehler”, “Abweichungen” und “Unfälle.” Sicherheit entsteht durch Wechselwirkungen zwischen Systemkomponenten; sie ruht nicht in einer Person, einem Apparat oder einer Abteilung. Die Verbesserung der Sicherheit hängt ab von der Erkenntnis, wie Sicherheit aus dem Zusammenwirken der einzelnen Komponenten des Systems entsteht. Patientensicherheit ist ein Bestandteil der Qualität des Gesundheitswesens.[1]
Positive predictive value PPV	Positiver prädiktiver Wert PPV	Die Wahrscheinlichkeit, dass ein positives Resultat tatsächlich positiv ist.[9] *true positives / (true positives + false positives) x100%*
Potential adverse drug event	Beinahe-Arzneimittelereignis	Ereignisse, bei denen ein Schaden trotz eines Medikationsfehlers ausgeblieben ist, sind Beinahe-Arzneimittelereignisse. Ereignisse, bei denen durch Korrektur des Fehlers ein Arzneimittelschaden verhindert werden konnte, zählen ebenfalls zu den Beinahe-Ereignissen.[3;4]
Preventable adverse drug event	Vermeidbares unerwünschtes Arzneimittelereignis	Eine unerwünschte, aber vermeidbare Wirkung, zurückzuführen auf die Anwendung oder Verabreichung eines Medikaments.[3;4]

Begriff Englisch ***Abkürzung***	**Begriff Deutsch** ***Abkürzung***	**Erklärung**
Preventable adverse event	Vermeidbares unerwünschtes Ereignis	Ein unerwünschtes Ereignis, das auf einen Fehler zurückzuführen ist. Ein vermeidbares unerwünschtes Ereignis hat eine Schädigung zur Folge, die das Ergebnis einer medizinischen Behandlung ist und vermeidbar gewesen wäre.[3;4] Vorkommnisse, die möglicherweise, aber nicht zwangsläufig zu einem konsekutiven Schaden für den Patienten führen. Als vermeidbar sind unerwünschte Ereignisse dann einzustufen, wenn sie durch Einhaltung der zum Zeitpunkt des Auftretens geltenden Sorgfaltsregeln zu verhindern gewesen wären.[1]
Preventable death	Vermeidbarer Todesfall	Todesfälle, die auf eine unsachgemässe medizinische Behandlung zurückzuführen sind.[3;4]
Risk	Risiko	Sowohl die Durchführung wie auch das Unterlassen von Interventionen beinhalten ein Risiko, das durch den Behandler selbst bei sorgfältigster Beachtung nicht auszuschließen ist.[1]
Risk management	Risikomanagement	Risiko Management ist eine Prozessanalyse im Behandlungsumfeld mit dem Ziel, Risikosituationen mit möglichen mediko-legalen Konsequenzen aufzudecken, bzw. eine Managementmethode, die das Ziel hat, in einer systematischen Form Fehler und ihre Folgen - zu erkennen - zu analysieren und - zu vermeiden.[1]
Root cause analysis	Ursachen-Analyse	In der Fehlerforschung geht man davon aus, dass Incidents wie auch Unfälle / Fehler gleiche Ursachen (Wurzeln = Roots) haben. Somit kann man durch die Evaluation von Incident Reporting sowie durch Unfallanalysen auf gemeinsame Ursachen für System-Mängel stoßen.[1]
Sensitivity	Sensitivität	Sensitivität bezeichnet das Verhältnis zwischen positiven Testergebnissen und den tatsächlich positiven Ereignissen. Im Rahmen eines medizinischen Tests bezieht sich die Sensitivität auf den Anteil Personen, welche ein positives Testresultat für eine Krankheit aufweisen in einem Kollektiv von Personen, die tatsächlich krank sind. Kein Test hat eine 100%ige Sensitivität, weil einige kranke Personen negative Testresultate aufweisen (=falsch negative Testresultate).[9] *true positives / (true positives + false negatives) x 100%*
Specificity	Spezifität	Die Spezifität eines Tests beschreibt den Anteil an richtig negativen Resultaten, den der Test entdeckt, verglichen mit allen Patienten ohne die zu diagnostizierende Erkrankung.[9] *true negatives / (true negatives + false positives) x 100%*
Standard	Standard	Standard in der Medizin repräsentiert den jeweiligen Stand naturwissenschaftlicher Erkenntnis und ärztlicher Erfahrung, der zur Erreichung des ärztlichen Behandlungszieles erforderlich ist und sich in der Erprobung bewährt hat, demnach ist der Standard eine normative Vorgabe qualitativer und/oder quantitativer Art bezüglich der Erfüllung vorausgesetzter oder festgelegter (Qualitäts-) Anforderungen.[1]

ABBREVIATIONS

2-RN-check	double-check by nursing
ACS	acute coronary syndrome
ADE	adverse drug event
ADR	adverse drug reaction
AE	adverse event
AI	adverse incident
AIDS	Acquired Immune Deficiency Syndrome
AkdÄ	German Physicians' Association
AO	adverse outcome
aPTT	activated partial thromboplastin time
ASHP	American Society of Health System Pharmacy
AV	arteriovenous
av	atrio-ventricular
C	correct
CBC	complete blood count
CERT	Center for Education and Research on Therapeutics
CH	chart review
CHE	Switzerland
CI	confidence interval
CIRS	critical incident reporting system
CJD	Creutzfeldt-Jakob disease
CL	clearance
CNS	central nervous system
CPOE	computerized physician order entry
CT	computerized tomography
CUDA	UCSF medical center inpatient pharmacy
CYP	cytochrome P450 enzyme
DDI	drug-drug-interaction
DRP	drug-related problem
ECG	electrocardiogram
eIR	encouraged / solicited incident reporting
EPS	extrapyramidal symptoms
ER	extended release
f	female
FDA	The United States' Food and Drug Administration
FIN	Finland
FTE	full-time employee
HCl	hydrochloride
hr	hour
hrs	hours
ICSR	individual case safety report
ID	identification
IHI	Institute for Healthcare Improvement
IM	intramuscular
INR	international normalized ratio
IOM	Institute of Medicine
IR	incident report / incident reporting
ISMP	Institute for Safe Medication Practices
IU	international units
IV	intravenous
IVAS	intravenous additive services (pharmacy department)
κ	Kappa value
kg	kilogram (bodyweight)
L	liter
lab	laboratory
LPN	licensed practical nurse
m	male
MD	medical doctor
ME	medication error
MedMarx	Internet-based program to report, track, and share medication error data
med	drug / medication
med rec	medication reconciliation

MedWatch	FDA's safety information and AE reporting program
mg	milligram
min	minutes
mL	milliliter
MRI	magnetic resonance imaging
msec	millisecond/s
N	number (statistical)
NA	not applicable
NCCMERP	The National Coordinating Council for Medication Error Reporting and Prevention
NLD	The Netherlands
NR	not reported
OB	direct observation
ok	okay, e.g. tested
P&T	pharmacy & therapeutics
PAB	peripheral arterial bypass
PCA	patient controlled analgesia
PCP	primary care provider
pharmCH	review of prescription charts by a pharmacist
PharmD	pharmaceutical doctor
physIR	incident reporting by a physician
pIR	patient incident reporting
Plts	platelets
PO	oral
PPV	positive predictive value
premed	premedication
PRN	as needed (Latin: pro re nata)
PSI	patient safety incident
PT	prothrombin time
PTT	partial thromboplastin time
Pyxis	Brand of an automated drug dispensing cabinet system
QTP	QT prolongation
QTc	QT corrected for heart rate
RBC	red blood cell count
RN	regular nurse
ROR	reporting odds ratio
SD	standard deviation
sex.	sexually
STEMI	ST-segement myocardial infarction
TDM	therapeutic drug monitoring
TdP	torsades de pointes
TR	trigger tool
TTH	time to hemostasis
U	unclear
UMC	Uppsala Monitoring Center
US(A)	United States of America
UCARE	electronic clinic information system
UCSF	University of California San Francisco
UE	unintended event
UFH	unfractionated heparin
VAS	visual analog scale
W	wrong
WBC	white blood cell count
WHO	World Health Organization
WHO-ART	The World Health Organization's adverse reaction terminology
wks	weeks
X	not ordered
X/X	number / total number
Y/N	yes or no answer

INTRODUCTION

The Institute of Medicine (IOM) report „To Err is Human“, published in 1999, alerted health care institutions worldwide to the necessity of a strategic approach to reduce medical errors.[10] Although the report focused on the United States (US) health care system, it provided in-depth analysis of a wide range of universal patient safety concerns.[11]

A major focus of the report was aimed at drug-related problems (DRPs), encompassing adverse drug reactions (ADRs) and medication errors (MEs).[10] Medication errors represent the major fraction of DRPs.[12] Although absolute numbers of their frequency and related cost is difficult to characterize, they pose a significant social and economic burden. Based on investigations by the Swiss Foundation for Medication Safety and on international scientific publications, it is estimated that up to 4% of all hospital admissions in Switzerland are due to DRPs, and that at least 7.5% of all Swiss inpatients experience an ADR and/or a ME.[13;14] The additional costs associated with these errors has been estimated to be up to 100 million dollars per year for a university hospital in Switzerland.[15]

Approximately a quarter of DRPs are preventable,[16] thus health care institutions must develop a strategic approach to decrease DRPs and improve patient safety.[11] Professional organizations, including the American Pharmacists Association stress the importance of interdisciplinary teams to comprehensively address medication safety.[17] Based on their comprehensive education, pharmacists are well-suited for an active role in the ME reduction.[17] Clinical pharmacists provide added value by participating in multidisciplinary teams, and their interventions reduce preventable adverse drug events and prescribing errors, resulting in cost savings.[18-22]

In addition to the previously described clinical pharmacy activities, a new role for hospital pharmacists, the medication safety officer, is emerging, primarily in the US. The medication safety officer is responsible for the management of all medication use safety and continuous quality improvement plans. Essential job functions include patient and medication safety, staff development / training and medication use improvement.[23] Established organizations, including the American Society of Health-System Pharmacists (ASHP) and the Institute for Safe Medication Practices (ISMP) strongly recommend one full-time employee per hospital entirely dedicated to the reduction of DRPs and the improvement of medication safety.[24;25]

Medication safety issues are often identified via postmarketing pharmacosurveillance. In most instances, drugs have received approval based upon trials involving only certain patient populations. Pediatric or geriatric patients, women of childbearing age and patients with certain concomitant diseases are often excluded from clinical trials, although they are treated with these substances in daily practice nevertheless.[26] Consequently, it is not surprising that some of these excluded groups are often those in whom unanticipated postmarketing adverse drug events are identified.
Medication safety surveillance in the post-marketing phase is often limited to regulatory pharmacovigilance activities.[27] Spontaneous reporting systems for ADRs have been the cornerstone of signal detection in pharmacovigilance for the last four decades. However, it is well known that some adverse effects of drugs are detected too late, only after many patients have been exposed. The need for earlier detection and a more proactive approach are strongly recommended in Europe and in North America.[28] However, individual hospitals have an additional need for institution-specific assessments of DRPs.

The aims of this thesis are to 1) Describe Swiss hospital pharmacists' perceptions of their current and future role in medication safety and 2) Identify efficient tools to allow hospital pharmacists to proactively address medication safety.

As a starting point, a survey was performed to evaluate current hospital pharmacist activities contributing to medication safety (Chapter 1).
An internet-based tool was used to compose, distribute and analyze questionnaire-based surveys.

Subsequently, commonly used or recommended methods were identified from the current literature for medication safety assessment and evaluated for potential application in the Swiss hospital pharmacy setting.

Chapter 2 suggests structured approaches to a systematic literature review in order to assess the safety of active substances and drug products. The American Society of Health-System Pharmacists (ASHP) provides a number of recommendations to manage drug use in the inpatient setting. These include a multidisciplinary pharmacy & therapeutics committee, meeting regularly under a defined constitution, as well as the appropriate management of the drug formulary.[29;30] An objective evaluation and selection process, using peer-reviewed publications is an important component for safe medication management.[30-32]

Once a product is chosen for formulary addition, regular medication use evaluations (MUEs) must be performed.[33] Chapter 3 evaluates the most commonly recommended medication safety assessment methods in the literature for assessment of medication safety.[34]

The Institute for Healthcare Improvement (IHI) specifically recommends the trigger tool or indicator technology in the identification of medication errors.[35] Chapter 4 describes the development, piloting and use of a manual trigger tool process for unfractionated heparin.

A method complementary to the trigger tool methodology is incident reporting.[34] However, due to the widespread underreporting, this technique does not offer a comprehensive picture of a drug's safety profile.[2;36;36;37]
Alternatively, organizations systematically collecting critical incident reports like the US Food and Drug Administration (FDA) or the World Health Organization (WHO) can be accessed. The methodological approach to the evaluation of pharmacovigilance systems as well as the information obtained is discussed in chapters 5 and 6, addressing the controversy around the use of the antipsychotic haloperidol.

CHAPTER 1

Medication safety activities in Swiss hospitals:

A status report on the role of the hospital pharmacist

This chapter has been published in an abbreviated format in:
The European Journal of Hospital Pharmacy EJHP 2010, volume 16, issue 6. page 54-55.

ABSTRACT

Background

The role of hospital pharmacists in Switzerland has changed significantly over the past decade. Initially focused upon activities associated with the timely dispensing of drugs, the position has evolved into different specialties, including medication safety.

Objective

The aim was to investigate the role of the hospital pharmacists in medication safety improvement.

Method

An online survey (www.surveymonkey.com) containing 22 questions was sent to 41 Swiss pharmacy directors. The questions addressed 4 sections: demographic information, current medication safety, clinical pharmacy activities, and future medication safety-relevant activities.

Results

Twenty-six of 41 questionnaires were returned (response rate 62%).
The hospitals (184 to 2000 beds) employed an average of 0.76 pharmacist full-time employees (0.33 - 1.94 FTEs) per 100 beds (European average: 1 FTE per 100 beds). In 23 of 26 hospitals (88%) a constant pharmacy & therapeutics committee was in place. Additional committees addressing medication safety were active in 17/25 hospitals (65%). Twenty-four of 26 hospitals (92%) maintained a critical incident reporting system. In 12/26 institutions (46%), the pharmacy was responsible for pharmacovigilance. Clinical pharmacy was established to some degree in 25/26 hospitals (96%) Other medication safety activities were ongoing in 22/26 institutions (85%), including the implementation of eHealth tools (11/22 hospitals, 50%) and increasing the scope of clinical pharmacy services in 4/22 hospitals (18%).

Conclusion

Swiss hospital pharmacists are proactively supporting medication safety initiatives.
However, staffing, which is lower in Swiss hospital pharmacies than the European average, must be increased to allow for adequate proactive medication safety activities. Future activities appear to be primarily focused on e-health technologies. In order to monitor the future trends, the survey should be repeated on an annual basis.

INTRODUCTION

The role of hospital pharmacists in Switzerland has changed significantly over the past decade. First focusing on the timely dispensing of medication the hospital pharmacists has evolved into different specialties. From logistics, production, to analytics, clinical services and patient counselling, the hospital pharmacist has begun to navigate in an increasingly interdisciplinary field. There is strong consensus that hospital pharmacists can significantly contribute to medication safety from admission to discharge.[18;19;21;22;38-44]

In the US, pharmacists are increasingly acknowledged as leaders in the field of medication safety.[45] The Institute for Safe Medication Practices (ISMP), The American Society of Health-System Pharmacists (ASHP), and other US organizations advancing medication safety, are promoting the role of the medication safety officer (or medication safety systems manager) through strategic initiatives and education.[46-48]

The medication safety officer is intended to be a key member of the health care team, coordinating all activities related to patient safety and quality improvement in the medication use process.[48] ASHP offers guidelines for residencies in medication-use safety, enabling pharmacy graduates to transition from generalist practice to a specialized role as an organizational leader in the achievement of medication-use safety.[47] As of 2010, the American Society of Medication Safety Officers (ASMSO) listed 500 members, representing nursing, pharmacy and medicine.[49]

Although the prevalence of drug-related problems (DRPs) in Swiss hospitals is difficult to quantitate, it is estimated that 7.5% of medical inpatients experience at least one DRP during their hospital stay and that 0.4% of the events are associated with a medication error (ME).[14;50] Approximately 4% of patients are admitted to the hospital because of a DRP, leading to direct annual extra costs of 70–100 million Swiss francs.[15;50;51]

Consequently, the proactive involvement of Swiss hospital pharmacist in medication safety is a logical next step both from a patient safety point of view and from an economical perspective.

This chapter evaluates the current activities of Swiss hospital pharmacists in medication safety activities and proposes a questionnaire to assess the current state of the art.

METHODS

An online survey with 22 questions was developed using the tool “SurveyMonkey” (www.surveymonkey.com).

The concept of the survey was based on the ASHP survey of national hospital practice executed[52-54] and the publication by Longo et al.[11]. The questions were compiled in collaboration with the Swiss Patient Safety Foundation.

The survey consisted of four major sections:

1. Demographic information (hospital and hospital pharmacy / staffing)
2. Drug and medication safety activities
3. Clinical pharmacy activities
4. Future prospects of medication safety activities

An overview of the questions presented in this survey is available in appendix 1 at the end of this chapter.

The Swiss Hospital Pharmacists’ Association GSASA provided a list of all Swiss hospital pharmacy directors.

The survey was sent out to 41 directors of pharmacy, representing 41 hospitals in three language regions of Switzerland.

Twenty-nine hospitals (71%) were located in the German speaking part, 10 (24%) in the French speaking part and 2 (5%) in the Italian speaking part. Therefore, the invitation letter was sent out in German, French and Italian. The survey itself was available in English and German in order to reduce the translation effort and to make the survey internationally approachable.

A reminder to participate in the survey was sent out after three weeks.

The results were transferred to an Excel file and analysed using descriptive statistics.

RESULTS

After the second reminder, 26 of 41 surveys (63% response rate) were returned.
Twenty-three participants (88%) used the German questionnaire, while 3 (12%) used the English version.

Demographic information

The 26 participating hospitals maintained an average of 632 beds (184 – 2000 beds).
The following hospital sizes were represented:

- ≤ 200 beds: 2 hospitals
- > 200 - ≤ 400 beds: 7 hospitals
- > 400 - ≤ 600 beds: 7 hospitals
- > 600 - ≤ 800 beds: 4 hospitals
- > 800 - ≤ 1000 beds: 4 hospitals
- > 1500 beds: 2 hospitals

Different types of hospitals were represented in the survey:
University hospitals (3/26, 12%), cantonal hospitals (10/26, 38%), regional hospitals (5/26, 19%), private hospitals (3/26, 12%), hospital networks or groups of hospitals serviced by a central pharmacy (4/26, 15%), and one city hospital (1, 4%).
The hospital pharmacies participating in the survey employ from 1 to 17 pharmacists, corresponding to 1 to 12 full-time equivalents (FTEs). This results in an average of 0.76 pharmacist FTEs (0.33 - 1.94 FTEs) per 100 beds. Two participants did not answer personnel-related questions.

Service information

In 25 of 26 hospital pharmacies (96%), 1 pharmacist is present in the hospital pharmacy during at least 8 hours every working day (excluding weekends and public holidays). A pharmacist is always available by telephone in all 26 hospitals during regular working hours.
Fifteen of 26 hospital pharmacies (60%) offer a 24/7 emergency service. One pharmacy (8%) offers extended, albeit not around-the-clock services, 3/26 pharmacies (12%) have a pharmacist available on the phone and 6/26 pharmacies (23%) do not offer on-call services. One participant did not specify. Designated personnel other than pharmacy employees have access to the pharmacy in emergency situations in the absence of regular pharmacy personnel in 15/26 hospitals (58%).

Drug supply

While 2/26 hospital pharmacies (8%) offer unit dosing, 24/26 pharmacies (92%) supply drugs to satellite pharmacies on the wards, where nursing is responsible for the preparation and distribution of drugs to individual patients.

In 3/26 hospitals (12%) pharmacy technicians are directly involved in drug distribution processes. Although automated dosing cabinets are used in Switzerland, none of the participating hospitals employed this technology.

Participation in committees associated with medication safety

A pharmacy & therapeutics (P&T) committee was in place in 23/26 hospitals (88%) at the time of the survey. In 2/26 institutions (8%), the pharmacy determined those medications which are available at the hospital; physicians were contacts for expertise as needed for decision making. One pharmacist did not answer this question.

Of the 23 institutions with an established P&T committee, a pharmacist chaired the P&T committee in 20/23 (87%) and co-chaired it in 2/23 institutions (9%). In one case, the function was not specified.

Seventeen of 26 institutions (65%) reported additional committees concerned with medication safety where pharmacists were involved: quality management and risk assessment committees (6/17 hospitals, 35%), critical incident reporting committee (5/17, 29%), medication safety committee (2/17, 12%), hygiene committee, antibiotics committee, pharmacovigilance committee, and pharmacy-nursing-exchange committee (1 hospital each, 6%).

Critical incident reporting system (CIRS)

Twenty-four of 26 hospitals (92%) maintain a CIRS of which 22/24 (92%) allow for anonymous reporting. Eighteen of 24 institutions (75%) offer electronic reporting. In 4/24 institutions (17%), the pharmacy is responsible for the CIRS, in 5/24 cases (21%), it is a physician's responsibility, and in 16/24 cases (67%) the centralized quality management handles the CIRS.

In 12/26 institutions (46%) the pharmacy was responsible for post-marketing surveillance (pharmacovigilance) of the drugs used in the hospital. In the other institutions it was either the pharmacology department (2/26 hospitals, 8%), the P&T committee (2/26, 8%), or quality management (1/26, 4%). In 4/26 institutions (15%), there was no definite standard operating procedure on pharmacovigilance and 5/26 insitutions (19%) did not specify their policy.

Medication safety literature

Different sources were used for medication safety issues. The 5 most used sources aside from in-house CIRS analysis (60%) were information sent out by the regulatory drug agency (80%), scientific journals (76%), pharmavista information service (64%, www.pharmavista.ch), the FDA homepage (48%) and subscriptions to medication safety newsletters (36%). Five pharmacy directors were familiar with the ISMP homepage (www.ismp.org).

Medication safety activities

Different medication safety projects involving hospital pharmacists were ongoing at the time of the survey in 22/26 institutions (85%): eleven of 22 hospitals (50%) were implementing computerized physician order entry (CPOE) and/or the establishment of an electronic patient record, 4/22 hospitals (18%) were increasing the scope of clinical pharmacy activities, 3/22 hospitals (14%) were promoting their CIRS and 1 hospital (5%) was in the process of creating a patient safety committee. Three of 22 projects (14%) were not specified.

Clinical pharmacy services were established to some degree in 25/26 hospitals (96%, 1 respondent skipped the question). All respondents (25/25, 100%) offered a drug information system by phone or email. Twenty-one of 25 institutions (84%) offered consulting for drugs administered through a feeding tube. Drug interaction checking was performed in 17/25 hospitals (68%) upon request. Rounding with physicians was established in 16/25 institutions (64%). Chart review was performed in 5/25 hospitals (20%). Therapeutic drug monitoring (TDM) was done in 4/25 hospitals (16%). One hospital (4%) offered full medication reconciliation on admission and at discharge, while another hospital (4%) only offered this service on admission. No patient teaching is done in any of the 25 hospitals answering this question.

The 4 services most often targeted by clinical pharmacy were medicine (68%), geriatric care (42%), surgery (31%) and intensive care (31%).

Patient relevant data: access and availability

The access of the pharmacy to patient-related information as well as the electronic availability of data is displayed in Table 1. Only one of 26 pharmacies reported no access to patient-related data 4%). Two of 26 pharmacy directors (8%) stated that they have access to an individual patient's information on a case per case basis.

Medication safety perspective

Detailed information regarding the perception of the hospital pharmacy directors on the future development of medication safety is displayed in Table 2. In regard to the future development of medication safety related activities (24 respondents), the following projects were considered most important: the expansion of the IT-infrastructure including electronic prescribing, electronic patient record, automated dispensing, and clinical decision support (23/24 hospitals, 96%) and the expansion of clinical pharmacy services (19/24, 79%).

Tools most possibly considered for use in medication safety activities among 24 respondents were direct observation of medication-related processes on the wards (23/24, 96%), analysis of the CIRS system (20/23, 83%), and chart review (16/24, 67%). Surveys (questioning health care professionals or patients using phone, email or paper-based questionnaires, 7/24, 29%), analysis of MedWatch-data (Swissmedic, WHO or FDA, 8/24, 33%), and trigger tool / indicator technology (9/24, 38%) were less popular. Of the respondents, 9/24 (38%) were not familiar with the trigger tool / indicator technology.

When queried regarding the future role of the hospital pharmacist in medication safety improvement, pharmacy directors requested improved interdisciplinary collaboration particularly focusing on transition of care. Expanding the role of the hospital pharmacist to be a medication safety specialist was strongly recommended.

Table 1: Current medication safety activities in Swiss hospitals in relation to the hospital size and pharmacist staffing

DEMOGRAPHIC INFO			SERVICE	COMMITTEES			CIRS		CLINICAL PHARMACY ACTIVITIES		DATA ACCESS			
Number of beds	Number of hospitals [N]	Mean number of pharmacists per 100 beds	24/7 pharmacy emergency services	P&T committee	P&T committee: pharmacist chair / co-chair	Other committees addressing medication safety issues	CIRS	CIRS electronic	Clinical activities: rounding with physicians	Clinical activities: TDM	Data access: drugs on admission	Data access: drug prescriptions	Data access: lab values	Data access: drugs at discharge
≤ 400	**9**	0.68	4 (44%)	8 (89%)	9 (100%)	7 (78%)	8 (89%)	6 (67%)	5 (56%)	2 (22%)	3 (33%)	6 (67%)	6 (67%)	3 (33%)
> 600 - ≤ 800	**11**	0.75	6 (55%)	9 (82%)	9 (82%)	7 (64%)	10 (91%)	6 (55%)	6 (55%)	1 (9%)	5 (46%)	6 (55%)	4 (36%)	3 (27%)
> 800	**6**	0.62	5 (83%)	6 (100%)	4 (67%)	3 (50%)	6 (100%)	6 (100%)	5 (83%)	1 (17%)	3 (50%)	6 (100%)	3 (50%)	4 (67%)

Abbreviations: CIRS = critical incident reporting system, lab = laboratory, P&T = pharmacy & therapeutics, TDM = therapeutic drug monitoring

Table 2 Access to and availability of patient relevant data

Type of data	Information available electronically		Information available to the pharmacy	
	% of institutions	Number of institutions N = 26	% of institutions	Number of institutions N = 26
medication on admission	35%	9	42%	11
medication at discharge (prescription)	46%	12	38%	10
lab data	81%	21	50%	13
prescriptions	35%	9	58%	15
nursing documentation	50%	13	50%	13
drug dispensing	12%	3	15%	4
physical examination report (e.g., radiology, CT, MRI)	77%	20	38%	10
procedure report (e.g., surgery)	58%	15	35%	9
discharge summary	69%	18	42%	11
incident reports / sentinel events	42%	11	27%	7

Abbreviations: CT = computer tomography, lab = laboratory, MRI = magnetic resoncance imaging

Table 3 Importance of future medication safety activities

ACTIVITIES	RATING (24 respondents) [number of pharmacy directors]			RATING – IMPORTANCE very important: 2 points potentially important: 1 point not important: 0 points
	very important	potentially important	not important	
expansion of the IT-infrastructure (electronic prescribing, electronic patient record, automated dispensing, clinical decision support)	23	1	0	47
expansion of clinical pharmacy	19	5	0	43
medication safety education of other health care professionals (e.g., nurses, physicians)	12	12	0	36
increase the level of activity in the pharmacy & therapeutics committee	14	7	3	35
intensification of pharmacovigilance	12	9	3	33
expand the hospital pharmacy team	10	12	2	32
publication of a pharmacy newsletter	7	16	1	30
centralized production / reconstitution of parenteral drugs	8	14	2	30
addition of content to the printed drug list / intranet page	8	12	4	28
foundation of a medication safety committee	8	12	4	28
patient education	4	14	6	22
introduction of a unit dose system	1	12	11	14
extend the pharmacy opening hours	0	12	12	12
expand the emergency service of the hospital pharmacy	1	10	13	12

DISCUSSION

As reported in “To Err is Human”, DRPs are significant patient safety issues.[7] Consequently, medication safety must be assessed regularly and strategies must be developed to address preventable DRPs.[43;55]

As this survey demonstrated, pharmacy staffing in Switzerland is limited with an average of 0.76 pharmacist FTEs per 100 beds. In addition, an unknown number of primarily smaller hospitals have only consultancy services available through a public pharmacy and no in-house hospital pharmacist. Pharmacy technicians or nursing staff are responsible for the provision of pharmacy services. Supervision is provided by an external community pharmacist, irregularly attending on site.

Similar problems are faced in other European countries: an average of 1 FTE per 100 beds is assigned to a pharmacist, only 0.3 FTEs per 100 beds exists in Germany.[56] Bond et al. identified a direct relationship between the number of medication errors and staffing.[57] Factors associated with decreased medication errors included drug information services, clinical research, adverse drug reaction management, medical rounds participation, drug admission histories, and increased clinical pharmacist staffing. The two most important variables toward reduction of medication errors were pharmacist-conducted drug histories and increased staffing levels of clinical pharmacists.[57]

A comprehensive program intended to improve the status of health-system pharmacy practice is the “ASHP 2015 Health-System Pharmacy Initiative”.[58]

Hospital pharmacist should promote the introduction of e-health technologies[59;60] and proactive medication safety assessment methods. [61] However, institutional commitment and leadership is critical toward the establishment of a successful culture of medication safety.[28]

Increased clinical pharmacy activities with associated outcomes are crucial for medication error reduction.[57] Consequently, the following chapters focus on research tools for hospital pharmacists to allow for evidence-based drug therapy.

As per the American Society of Health-System Pharmacists, a sound formulary, managed by the pharmacy & therapeutics committee is a key cornerstone to evidence-based drug therapy.[29;30]

In the next chapter, two examples of evidence-based reviews for formulary considerations are given.

APPENDIX 1 TO CHAPTER 1

Original Survey

Page 1

1. Introduction

Dear colleagues

At the moment, hospital pharmacists gain importance internationally as specialists for comprehensive medication safety activities, as actual scientific publications show.
Specifically in the US, institutions staff the new position of a "medication safety officer". Organizations like the "Institute for Safe Medication Practices" (www.ismp.org) promote this new function. Based on their education and position in health care institutions, hospital pharmacists are optimally suited for this new role.

My PhD thesis, supported by Prof. Christoph Meier (University of Basel) and Prof. B. Joseph Guglielmo (University of California San Francisco), is assessing the current and future role of hospital pharmacists in medication safety. In addition, we are specifically interested in the evaluation of suitable tools for the effective and efficient analysis of medication safety in an individual institution and subsequent improvement projects.

For our research project, we would like to assess the current role of Swiss hospital pharmacists in medication safety activities in their institutions and learn about their ideas for the future.
Therefore, we would like to ask you to participate in the following survey, investigating your involvement in medication safety activities. The survey, sent out to all Swiss directors of pharmacy, requires approximately 20 minutes of your time.
Please feel free to answer the questions in either German, French, Italian or English.

I remain at your service for questions and additional comments.
Thank you very much for your collaboration,
Carla Meyer-Massetti
hospital pharmacist FPH
carla.meyer@unibas.ch

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2. Demographic information

1. Number of beds in your institution:

2. The type of hospital you are working for

❍ a university hospital

❍ a cantonal hospital

❍ a regional hospital

❍ a private hospital

❍ other:

3. The size of your pharmacy

Number of active pharmacists:
Full-time equivalents of your pharmacists:
Number of pharmacy technicians / chemists:
Number of other employees:
Full-time equivalents of ALL employees in the hospital pharmacy:

4. At least 1 pharmacist is present in the hospital for at least 8 hours per day.

❍ yes

❍ no

❍ sometimes

Comment:

5. The hospital pharmacy offers an emgergency service / on-call pharmacist.

❍ yes, 24 hours a day, 7 days a week

❍ yes; during specific hours (e.g. weekends, holidays).

❍ no

❍ sometimes

Comment:

6. When the pharmacy is officially closed, other health care professionals / employees of the hospital have access to the hospital pharmacy.

❍ yes; the pharmacy supervises and registers the access.

❍ yes; the pharmacy does NOT supervise and register the access.

❍ no

❍ sometimes

Comment:

7. Drugs arrive at the patient's bedside using the following technology:

❒ patient-specific unit-dose directly from the pharmacy

❒ drugs are prepared and dispensed by nursing

❒ pharmacy-technicians are involved in the process on the wards

❒ automated dispensing systems (e.g., Pyxis etc.) are used

❒ other system: :

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3. Drug & medication safety

1. Does your hospital maintain a pharmacy & therapeutics committee?

❍ yes

❍ no

❍ different answer:

2. What function in the pharmacy & therapeutics committee is assigned to the pharmacy?

❒ chair of the committee

❒ deputy chair of the committee

❒ regular member

❒ participation on demand

❒ other form of participation:

3. Are there other committees in your institution taking care of medication safety issues?

❍ yes

❍ no

If yes, please specify:

4. Does your hospital maintain an incident reporting system for medication errors and adverse drug events?

❍ yes

❍ no

5. Please indicate the characteristics of the incident reporting system at your hospital:

❒ anonymous

❒ non-anonymous

❒ paper-based

❒ electronic

❒ connected to a national MedWatch system

❒ at the responsibility of the pharmacy

❒ at the responsibility of the medical services (physician)

❒ at the responsibility of nursing

❒ at the responsibility of quality management / risk management

Comments:

6. Who is responsible for the pharmacovigilance in your institution?

❍ a hospital pharmacist

❍ the quality-management / risk management

❍ the pharmacology department

❍ a physician

❍ a nurse

❍ somebody else:

7. How do you remain up to date on medication safety issues?

❒ internal communications based on the institution's incident reporting system

❒ information issued by Swissmedic

❒ scientific literature

❒ Pharmavista® (www.pharmavista.net)

❒ FDA-homepage

❒ ISMP-homepage

❒ WHO-homepage

❒ newsletter subscription

❒ other sources (please itemize):

8. In which projects improving medication safety is the pharmacy involved?

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4. Clinical pharmacy

1. Please indicate the clinical pharmacy-related services your pharmacy provides:

❒ medication information service (phone, email)

❒ medication reconciliation on admission

❒ medication reconciliation at discharge

❒ patient education

❒ rounding (with physicians, nursing)

❒ chart-review

❒ interaction checking

❒ lists / instructions for drug application through a feeding tube

❒ blood level checks of specific substances

❒ pharmacovigilance activities

❒ other services / activities:

2. Which services are on the receiving end of your clinical pharmacy services?

❒ internal medicine

❒ geriatrics

❒ surgery

❒ orthopedic surgery

❒ radiology

❒ emergency services

❒ intensive care

❒ ambulatory care

❒ other departments:

3. What information is available electronically in your institution?

❒ medication on admission

❒ medication at discharge (prescription)

❒ lab data

❒ prescriptions

❒ nursing documentation (electronic patient record)

❒ drug dispensing (e.g., using Pyxis)

❒ physical examination report (e.g., radiology, CT, MRI)

❒ procedure report (e.g., surgery)

❒ discharge summary

❒ incident reports / sentinel events

❒ other information:

4. What information (electronic or paper-based) is accessible for the pharmacy?

❒ medication on admission

❒ medication at discharge (prescription)

❒ lab data

❒ prescriptions

❒ nursing documentation (electronic patient record)

❒ drug dispensing (e.g., using Pyxis)

❒ physical examination report (e.g., radiology, CT, MRI)

❒ procedure report (e.g., surgery)

❒ discharge summary

❒ incident reports / sentinel events

❒ other information:

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5. Future prospects

1. **Please rate the importance of implementing the following activities / services at your institution**

	very important	potentially important	not important
increase the level of activity in the pharmacy & therapeutics committee	❍	❍	❍
intensification of pharmacovigilance	❍	❍	❍

	very important	potentially important	not important
expansion of clinical pharmacy	❍	❍	❍
addition of content to the printed drug list / intranet page	❍	❍	❍
publication of a pharmacy newsletter	❍	❍	❍
patient education	❍	❍	❍
introduction of a unit dose system	❍	❍	❍
expansion of the IT-infrastructure (electronic prescribing, electronic patient record, automated dispensing, clinical decision support)	❍	❍	❍
centralized production / reconstitution of parenteral drugs	❍	❍	❍
medication safety education of other health care professionals (e.g., nurses, physicians)	❍	❍	❍
expand the hospital pharmacy team	❍	❍	❍
extend the pharmacy opening hours	❍	❍	❍
expand the emergency service of the hospital pharmacy	❍	❍	❍
foundation of a medication safety committee	❍	❍	❍
other activities:			

2. The implementation / application of which of the following tools would you consider if you were planning a medication safety project?

❒ analyzing the results of the internal incident reporting system

❒ trigger tool / indicator-technology

❒ (I'm not familiar with the trigger tool)

❒ analysis of MedWatch data (Swissmedic, WHO or FDA)

❒ observation of medication-related processes on the wards

❒ detailed analysis of patient records

❒ surveys (questioning health care professionals or patients using phone, email or paper-based questionnaires

❒ additional suggestions:

3. **Please describe briefly the future role of the hospital pharmacist in medication safety improvement as you personally imagine it:**

4. **Additional comments:**

Thank you very much for your valuable support!
Please don't hesitate to contact me with questions or comments.
Carla Meyer-Massetti
carla.meyer@unibas.ch or phone: 0041 43 243 76 28

CHAPTER 2

Evidence-based reviews for the comparative evaluation of drug products

Example 1:

Evidence-based review for the evaluation of a new opioid-analgesic (active substance. oxymorphone) considered for addition to the institution's formulary.

Example 2:

Evidence-based review of three stand-alone topical thrombins in order to decide on a replacement of the current product on the institutions formulary.

CHAPTER 2, Example 1

PHARMACY & THERAPEUTICS COMMITTEE
DRUG EVALUATION – SUMMARY PAGE

GENERIC NAME: Oxymorphone
PROPRIETARY NAME: Opana / Opana ER
THERAPEUTIC CLASS: Analgesic, Opioid

Salient Points:

Oxymorphone (Opana®) is an opiate analgesic approved for the treatment of acute and chronic moderate-to-severe pain after surgery, available in a rapid and delayed onset form as well as in an intravenous form. The oral formulation is being requested for formulary addition as a result of our comprehensive formulary review. The request for Opana® addition was based on the need to have an oral opiate with fewer adverse effects, especially reducing the burden of nausea and vomiting in patients treated with opiate analgesic drugs.

What is the efficacy of oxymorphone?

- Oxymorphone has an efficacy profile similar to that of other commonly used opiates.
- The quantity of existing comparative studies is very poor; there are only three published comparative studies in a hospital setting existent and one more in ambulatory care, treating chronic arthritis pain.
- No studies comparing oxymorphone to fentanyl or methadone are available.
- Existing studies are consistent, that the use of oral oxymorphone is as effective as various other comparator drugs (morphine, oxycodone, meperidine).
- Although initially oxymorphone has a rapid onset of action (30 minutes), it appears less effective than morphine with repeat doses (chronic therapy).
- In the three studies published to date, oxymorphone superiority with regard to efficacy was not observed.

What is the comparative safety of oxymorphone with comparator drugs?

- The adverse effects that have been observed with oxymorphone are similar to those seen with other mu agonists currently available on the US market. These include:
  - nausea
  - vomiting
  - sedation.
- In one study, when administered IV via patient controlled analgesia, oxymorphone caused significantly more nausea and vomiting (28%), when compared with morphine (9.5%) but less sedation (0.81 +/- 0.47 on a scale of 4) when compared with morphine (1.29 +/- 0.42 on a scale of 4)). These findings have not been confirmed in more recent studies.
- An overall advantage regarding nausea and vomiting wasn't observed.
- There are no studies available treating the abuse potential of oxymorphone compared to other opioids.

What are important aspects of oxymorphone regarding use in a hospital setting?

- Oxymorphone has a very rapid onset of action; however, formulary agents methadone and oxycodone do as well.
- Oxymorphone is not metabolized by the CYP 450 pathway; however, morphine provides a reasonable alternative.
- The influence of food on the absorption of oxymorphone is significant and enhances the absorption about 38%. This could be a critical issue especially when used as rescue medication.

Recommendations:

Therefore, given the available oral opiate options on the formulary and the lack of supporting literature demonstrating any advantage of this drug, we recommend Opana® not be added at this time.

PHARMACY & THERAPEUTICS COMMITTEE
DRUG EVALUATION

GENERIC NAME: Oxymorphone hydrochloride
BRAND NAME: OPANA®
THERAPEUTIC CLASS: Analgesic, opioid
Prepared by: Carla Meyer-Massetti, MSc
Candy Tsourounis, PharmD
UCSF Medication Outcomes Center
Department of Clinical Pharmacy

Table 4: Products in Class[62-67]

Generic	Brand	Manufacturer	FDA Approval
Oxymorphone hydrochloride	Opana	ENDO pharm	22/06/2006
Oxymorphone hydrochloride	Opana ER	ENDO pharm	22/06/2006
Methadone hydrochloride	Dolophine	RLI	08/13/1947
Morphine sulphate	MS contin	Purdue Frederick	05/29/1987
Oxycodone hydrochloride	Oxycontin	Purdue Pharma LP	12/12/1995
Fentanyl	Duragesic	ALZA	08/07/1990

INDICATIONS:
Table 5: FDA Labeled Indications[62-67]

Drug	Indication(s)
Opana (oxymorphone HCl)	Treatment of moderate-to-severe acute pain following orthopedic and abdominal surgeries, where the use of an opioid is appropriate.
Opana ER (oxymorphone HCl)	Treatment of moderate-to-severe acute pain in patients requiring continuous opioid treatment for an extended period of time. The drug is not intended for: - an “as needed” analgesic - for pre-emptive analgesia - pain in the immediate post-operative period (12-24 hrs following surgery for patients not previously taking the drug) - mild pain, that is not expected to persist for an extended period of time.
Dolophine (methadone HCl)	- For the treatment of moderate-to-severe pain not responsive to non-narcotic analgesics. - For detoxification treatment of opioid addiction (heroin or other morphine-like drugs). - For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.
MS contin (morphine)	Management of moderate-to-severe pain when a continuous opioid analgesic is needed. The drug is not intended for: - pain in the immediate postoperative period (12-24 hrs after surgery) for patients not previously taking the drug (reason: safety not established). - mild pain, that is not expected to persist for an extended period of time.
Oxycontin (oxycodone)	Management of moderate-to-severe pain when a continuous opioid is needed for an extended period of time. The drug is not intended for: - an “as needed” analgesic - pain in the immediate postoperative period (12-24 hrs after surgery) for patients not previously taking the drug (reason: safety not established).
Duragesic (fentanyl)	Management of persistent moderate-to-severe chronic pain. The drug is not intended for: - patients who are not opioid-tolerant - an “as needed” analgesic - management of acute pain for a short period of time - management of post-operative pain, including use after out-patient or day surgeries.

BACKGROUND:
The World Health Organization (WHO) developed a step-ladder approach to the management of pain. The WHO suggests the use of non-opioid analgesics initially; if pain persists or increases, and the addition of "mild opioids" for mild-to-moderate pain. If pain persists or increases further to moderato-to-severe, the use of strong, morphine-like analgesic drugs is recommended.[68]
After major surgery, the majority of patients experience moderate to severe pain. Opioid analgesics are considered a key component in the standard management of postoperative pain.[69] Patients are typically switched from parenteral opioids to oral opioids during 24 to 48 hours after surgery.[70]

Currently, the formulary includes several oral opioids as well as the transdermal patch:
- methadone HCl (Dolophine®)
- morphine HCl (MS contin®)
- oxycodone HCl (Oxycontin®)
- fentanyl (Duragesic®).

The Department of Anesthesiology wishes to include another oral opioid to the formulary: oxymorphone. In June 2006, an oral immediate release as well as a prolonged release form of oxymorphone were approved by FDA for the treatment of acute moderate to severe pain: Opana® and Opana ER®.[62;63] The intention of this request is to treat patients with a more potent opioid that causes fewer adverse side effects like nausea, vomiting and sedation.

Quantitatively, oxymorphone has tenfold less affinity to the κ receptor than the μ or σ receptor. The advantages of the σ affinity may be twofold: agonist actions at the σ receptor potentiate μ-mediated analgesic effects. They also may lessen the development of tolerance. The decreased affinity for the κ opioid receptor may explain the decreased sedation seen in previous studies compared to morphine. This, however, has not been confirmed by recent trials.[71]

The aim of this review is to evaluate the clinical impact of the above mentioned pharmacokinetic data, assessing the following aspects:
- analgesic efficacy of oxymorphone compared to the opioids available on the formulary,
- incidence of adverse drug effects of oxymorphone compared to the opioids already available.

CLINICAL PHARMACOLOGY:
Oxymorphone hydrochloride is a semi-synthetic opioid analgesic. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression. The precise mechanism of the analgesic action is unknown. Specific central nervous system opioid receptors have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. The role that the opioid receptors play in the peripheral nervous system is unknown.[62]

Table 6: Pharmacology of comparator drugs[64-66]

Drug	Clinical Pharmacology
Dolophine (methadone HCl)	synthetic mu-opioid agonist with multiple actions similar to those of morphine (see MS contin) possible antagonist at the N-methyl-D-aspartate (NMDA) receptor (the contribution of NMDA receptor antagonism to methadone's efficacy is unknown)
MS contin (morphine)	pure opioid agonist principal therapeutic action: analgesia other pharmacologic effects: the same as with Opana® no ceiling effect expected
Oxycontin (oxycodone)	
Duragesic (fentanyl)	pure opioid agonist, affecting predominantly the mu receptor principal therapeutic action: analgesia other pharmaceutical effects: the same as with Opana® **BLACK BOX WARNING: TRANSDERMAL USE IN OPIOID-NAÏVE PATIENTS**

PHARMACOKINETICS:
Like all pure opioid agonist analgesics, with increasing doses of oxymorphone there is increasing analgesia.[62]

Table 7: Pharmacokinetic data of oxymorphone and the chosen comparator drugs[62-67;72]

Parameters	Opana Oxymorphone HCl	Opana ER Oxymorphone HCl	Dolophine Methadone HCl	MS Contin Morphine	Oxycontin Oxycodone HCl	Duragesic Fentanyl
Dose (mg/day)	depending on pre-treatment and level of pain					
Bioavailability	10%		36 – 100%	40%	60-87%%	92%
Absorption	NA 38% higher with fatty food		30 – 60 min*	1.5 hrs	biphasic: 0.6 and 6.9hrs	according to the dosage indicated
Time to peak concentration	30 min	3 hrs (1 – 12 hrs)	1 – 7.5 hrs	3 – 4 hrs*	2.7 – 3.2 hrs	24-72 hrs
Volume of distribution	NA		1 – 8 L/kg	4L/kg	2.6L/kg	6L/kg
Effect of food	high influence dose prior or after eating		NA	NA, probably none	with high fat food	none
Active metabolite (s)	6-OH-oxymorphone		none	morphine-6-glucuronide	noroxycodone (oxymorphone)	none
Plasma protein binding	10% - 12% (20% - 40%)		85 - 90%	35%*	45%	79 - 87%
Steady-state level	after 3 days of multiple dosage		after days of regular dosing	after 1 day	24-36hrs	several 72 hrs applications
Half-life	single dose: 7.25 – 9.43 hrs multiple dose: NA	single dose: 9.35 – 11.30 hrs multiple dose: NA	8 - 59 hrs	2-4 hrs	4.5 hrs	17 hrs (13 – 22 hrs)
Renal Excretion	unchanged: < 1% total: 33 – 38%		mainly renal	enterohepatic	mainly renal	80%
CYP Substrate	none CYP2C9 and CYP3A4 slightly increased in vitro, no known effect in vivo		CYP3A4, CYP2B6, and CYP2C19 (CYP2C9 and CYP2D6)	none	CYP2D6 (for the metabolite oxymorphone)	CYP3A4

* Information not available in the packaging insert of the product.
Source: Swiss federal approved drug information www.kompendium.ch, April 2008, updated 11.2010[72]

Clinical Trials					
Sloan P et al. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study, Support Care Cancer 2005[70]					
Purpose **Design** **Duration (when specified)**	**Population** **Data Sources**	**Treatment**	**Measures/definitions**	**Results**	**Outcomes**
To assess the analgesic effectiveness and safety of the new oral oxymorphone ER formulation following treatment with morphine sulfate or oxycodone prospective, multicenter, multidose, open-label, sequential crossover study *[dose equivalence of oxymorphone compared to oxycodone and morphine not known at time of investigation]*	Population: N=86, no significant demographic and baseline pain differences present among groups • age 21 to 80 years • female 62% • white 86% Inclusion Criteria • adults age 18-80 years • history of chronic moderate-to-severe cancer pain • requiring at least oxycodone 20 mg or morphine 30 mg/day • stable analgesia (≤ 30% rescue medication within 3d) • pre-menopausal women not pregnant and sex. abstinent / contraception Exclusion Criteria • interference with absorption of study drug • hypersensitivity to the drug	Medications • oxymorphone ER 20mg [Opana ER] • morphine sulfate ER 15, 30, 60, 100 mg [MS contin] • oxycodone HCl 20, 40, 80 mg [Oxycontin] orally every 12 hrs use of other analgesics: none unless stable for 1 week before screening Treatment periods: • 3 days of titration with morphine or oxycodone When stable analgesia: • **period 1** 7 day treatment without dose adjustment • **period 2** crossover to 7 day treatment with oxymorphone in an equivalent dose Rescue medication: study medication in the IR form (10% of the daily dose) Exclusion criteria during the study patients unable to tolerate the assigned opioid were discontinued on this drug and treated with the alternate study drug	Effectiveness Patient records • analgesia • nausea • drowsiness • sleep quality • scheduled drugs • rescue medication Pain assessment • visual analog scale VAS 0 mm=no pain 10 mm excruciating pain • pain quality scale 0=no pain 1=mild pain 2=moderate pain 3=severe pain 4=excruciating pain • every 4 hrs from 8 am to 8 pm Adverse effects visual analog scale • 0 mm=no nausea 10 mm=severe nausea • 0 mm=no drowsiness 10 mm=extreme drowsiness Patient satisfaction 4 times VAS to assess least, worst and average pain during the previous 2 days Safety regular assessments of vital signs and adverse effects	Period 1 • insufficient therapeutic effect: oxycodone 30% morphine 15% Adverse effects No significant differences in VAS for nausea, drowsiness and quality of sleep. Patient satisfaction • no significant difference in pain relief among the three drugs • use of morphine rescue was twice as high as use of oxymorphone rescue ($P<0.05$) Safety Treatment with oxymorphone after treatment with either morphine or oxycodone had no clinically meaningful effect on vital signs, physical or laboratory parameters. Other findings linear dose relationships between oxymorphone and morphine as well as between oxymorphone and oxycodone were observed	• Oxymorphone ER and IR are effective for acute, moderate-to-severe pain. • Opioid rotation from morphine to oxymorphone was easily manageable. • Equivalent analgesia was obtained. • A linear relationship between oxymorphone and the two comparator drugs was observed.

Clinical Trials

Sinatra RS et al. A comparison of morphine, meperidine and oxymorphone as utilized in patient-controlled analgesia following cesarean delivery, Anesthesiology 1989[73]

Purpose **Design** **Duration (when specified)**	**Population** **Data Sources**	**Treatment**	**Measures/definitions**	**Results**	**Outcomes**
To compare efficacy, patient satisfaction and adverse effects of IV morphine, meperidine and oxymorphone in patients recovering from elective cesarean delivery. prospective, double-blind, randomized Duration = 24 hours	Population: N = 75 demographic variety and intraoperative anesthetic requirements statistically not significant Inclusion Criteria • healthy females • no history of drug / alcohol abuse (ASA PS I or II) • elective cesarean delivery • under epidural anesthesia Exclusion Criteria • severe respiratory depression during treatment Drop out during study period none	Treatment: 3 drug solutions containing 1ml each prepared by the pharmacy: • 1.5 mg morphine / ml • 15 mg meperidine / ml • 0.25 mg oxymorphone / ml Randomly assigned to the patient expressing pain **Loading dose:** Four 1 ml increments, 5 min apart (total: 6 mg morphine / 60 mg meperidine / 1 mg oxymorphone) Additional 1 ml increments until adequate analgesia **Self administration PCA:** 1.2ml boluses (equivalent to 1.8 mg morphine / 18 mg meperidine / 0.3 mg oxymorphone, max. every 8 min.	Data collection points: • first request • completion of loading • 1,2,4 hrs following PCA • then every 4 hrs - at rest - while moving Measures for: • pain intensity • satisfaction with drug 10-cm visual analog scale 0cm: no pain/very good 10cm: worst pain/very bad mild: VAS 1-3 moderate: VAS 4-6 severe: VAS 7-10 • total amount of drug • number of demands • number of PCA inject. • ratio injections/attempt • level of sedation 0= alert 1= drowsy, oriented 2= drowsy, nonconversant 3= very drowsy, disoriented • nausea & vomiting 0= none 1= occasional mild 2= occasional moderate • pruritus 0= none 1= mild 2= moderate Statistical analysis • covariance with Tukey and paired t test • Pearson r correlation • significance: P<0.5	Pain scores after loading dose Difference was not statistically significant. Amount of drug used Total dose requirements not statistically different; **BUT:** morphine was self-administered more often during the first 4 hrs of treatment. Number of rescue medication requests by PCA most frequent in the morphine group Ratio injections to attempts I:A • morphine significantly less than meperidine (p<0.05) • no difference between meperidine and oxymorphone Pain intensity a) Scores not statistically different at rest; **BUT:** • morphine: highest score in the first 4 hrs • meperidine: as morphine, but score isn't as high • oxymorphone: most rapid onset. **superior analgesia with oxymorphone during hrs 1 and 2, with morphine at hrs 12 and 24 (p< 0.05)** b) Scores while moving: more severe pain following meperidine IV (p<0.005) Patient satisfaction • Highest incidence of sedation, restlessness and anxiety: morphine (p<0.05) • Highest incidence of nausea / vomiting: oxymorphone (28%, p<0.05) • Best overall satisfaction: meperidine vs. morphine (p<0.05)	• Equianalgesic dosing with morphine, meperidine and oxymorphone is possible. • All drugs offered excellent pain relief. • Significantly higher doses of morphine were administered during the first 4 hrs of treatment because of the delayed onset. • Meperidine offered the best I:A ratio followed by oxymorphone. • Meperidine was least effective in controlling pain during movement. • Oxymorphone spared excessive discomfort during early hours, but was not as effective as morphine at later intervals. • The incidence of nausea was significantly higher in the oxymorphone group. • Satisfaction with morphine was lowest because of analgesic delay, level of sedation, need for supplemental analgesic.

Clinical Trials

Aqua K et al. Efficacy and tolerability of oxymorphone immediate release for acute postoperative pain after abdominal surgery: a randomized, double-blind, active- and placebo-controlled, parallel-group trial, Clinical Therapeutics 2007[69]

Purpose **Design** **Duration (when specified)**	**Population** **Data Sources**	**Treatment**	**Measures/definitions**	**Results**	**Outcomes**
To assess the efficacy and tolerability of multiple fixed doses of oxymorphone IR (immediate release) in the treatment of acute postoperative pain relief after orthopedic surgery. multicenter (21), randomized, double-blind, active- and placebo-controlled maximal 48 hours	Population: N=331 similar demographic data • women 98.8% • hysterectomies 80.1% • mean age: 42.6 (9.3) yrs Inclusion Criteria • men, women aged ≥18 yrs • women: no pregnancy, sex. abstinent or contraception • abdominal surgery • requiring an incision ≥3 cm After surgery: • hospitalization for ≥36 hrs • oral opioid therapy for ≥48 hrs • capability of swallowing Within 30 hours of surgery • moderate to severe pain after stopping IV opioids [scale: 1=none, 2=mild, 3=moderate, 4=severe] • pain intensity ≥ 50 mm [100mm visual analog scale; 0= no pain, 100= worst pain] Exclusion Criteria • laparoscopic surgery • lactating women • anticonvulsants within 4 wks • MAO inhibitors within 2 wks • long acting analgesics (12 hrs) efficacy endpoint median time to study discontinuation for all causes assessment of tolerability discontinuations due to treat-emergent adverse events (AEs)	Initial postoperative treatment short acting IM or IV opioid defined washout periods Four treatment groups • oxymorphone IR 10 mg • oxymorphone IR 20 mg • oxycodone IR 15 mg • placebo Two treatment schemes • single dose treatment 1 single dose of drug • multiple dose treatment 1 dose every 4 to 6 hrs upon request for 48 hrs Exclusion criteria during the study • *single and multiple dose treatment* need for additional analgesic within 4 hrs after study dose • *single dose treatment* need for additional analgesic 4 to 6 hrs after study dose: *switch to multiple dose treatment* • *multiple dose treatment* no need for additional analgesic at >6 hrs after previous dose	Two efficacy assessments • single-dose evaluation 6 hrs after the dose • multiple-dose evaluation 48 hrs after the dose Measures taken: • in the hospital: measured by hospital staff • if discharged: by patient diary and pill counting Pain assessments: • scale: 1=none, 2=mild, 3=moderate, 4=severe • pain intensity ≥ 50 mm [100 mm visual analog scale; 0= no pain, 100= worst pain] Time data points: 15, 30, 45, 60 minutes 2, 3, 4, 5, 6 hrs after dose Efficacy endpoint median time to study discontinuation for all causes Assessment of tolerability discontinuations due to treat-emergent adverse events Patient satisfaction at the end [scale: 1=poor to 5=excellent] Statistical analysis exactly defined	Efficacy • Oxymorphone IR 20 mg was significantly more effective over the 6 hrs-single-dose-evaluation (P<0.05). • Multiple dosing with active drugs has been significantly more effective than placebo (P<0.004 to P<0.005). • Average pain scores were significantly lower with active drugs compared to placebo (P<0.005). Discontinuation AEs did not differ significantly among active drug groups (P=NS): • oxymorphone IR 10 mg: 46.3% • oxymorphone IR 20 mg: 51.9% • oxycodone IR 15 mg: 54.2% • placebo: 34.1% Higher doses of oxymorphone were less well tolerated than lower doses. Median time to study discontinuation P <0.006 • oxymorphone IR 10 mg: 17.9 hrs • oxymorphone IR 20 mg: 20.3 hrs • oxycodone IR 15 mg: 24.1 hrs • placebo: 4.8 hrs Overall patient satisfaction no significant difference in "good to excellent" among active drugs: • oxymorphone IR 10 mg: 62.0% • oxymorphone IR 20 mg: 67.5% • oxycodone IR 15 mg: 67.5% significant compared to placebo (P<0.017) • placebo: 45.1%	• Administration of multiple doses of oxymorphone and oxycodone provided significant relief of pain. • Oxymorphone IR 10 mg and oxycodone IR 15 mg single dose were not significantly better than placebo in single doses. • Oxymorphone IR 20 mg single dose was effective vs. placebo. • A rigid dosing schedule is not appropriate using opioids. • Discontinuation rates were similar among groups. • Higher doses of oxymorphone caused slightly higher rates of AEs (not significant). • Nausea, vomiting and pruritus were more frequent in the active treatment group, especially for oxymorphone IR 20 mg & oxycodone IR 15 mg.

CONTRAINDICATIONS / WARNINGS:

Table 8: FDA labeled contraindications and warnings[62-67]

Contraindications	Opana Oxymorphone HCl	Opana ER Oxymorphone HCl	Dolophine Methadone HCl	MS Contin Morphine	Oxycontin Oxycodone HCl	Duragesic Fentanyl
Hypersensitivity	yes	yes	yes	yes	yes	yes
Respiratory depression	yes	yes	yes	yes	yes	yes
Bronchial asthma	yes	yes	yes	yes	yes	yes
Paralytic ileus	yes	yes	yes	yes	yes	yes
Hypercarbia	not mentioned	yes	yes	not mentioned	yes	yes
Interaction with alcohol	yes	yes	yes	yes	yes	yes
Head injury and increased intracranial pressure	yes	yes	yes	yes	yes	yes
Hypotensive effect	yes	yes	yes	yes	yes	yes
Anaphylaxis	not mentioned	not mentioned	not mentioned	yes	not mentioned	not mentioned
Hepatic impairment	yes	yes	yes	no	yes	unclear
Renal impairment	yes	yes	unclear	yes	yes	unclear

PRECAUTIONS:

Table 9: FDA labeled precautions[62-67]

Precautions	Opana Oxymorphone HCl	Opana ER Oxymorphone HCl	Dolophine Methadone HCl	MS Contin Morphine	Oxycontin Oxycodone HCl	Duragesic Fentanyl
Use in opioid-tolerant patients only	no	no	no	only 100mg, 200mg tablets	only 60mg, 80mg, 180mg	yes
Abuse potential -tolerance -physical dependence	yes	yes	yes	yes	yes	yes
Interactions with agonist/antagonists	yes	yes	yes	yes	yes	NA
Pre-existing heart disease	yes	yes	yes	yes	yes	yes
Biliary tract disease	yes	yes	yes	yes	yes	yes
Carcinogenicity	no (rats)	no (rats)	unclear	NA	no (assays)	no (assays)
Pregnancy	Category C	Category C	Category C	Category C	Category B	Category C
Lactation	not recommended	not recommended	not recommended for analgesia	not recommended	not recommended	not recommended
Pediatric use	not tested < 18 yrs	not tested < 18 yrs	not tested < 18 yrs	not tested	not tested < 18 yrs	yes (>2 years)
Geriatric use	dose reduction	dose reduction	unclear	unclear	reduced clearance	reduced clearance

ADVERSE EFFECTS:

Table 11: Adverse reactions reported in at least 2% of patients treated with Opana[62;63]

	OPANA (N=557) [%]	Placebo (N=270) [%]
Nausea	19.0	11.5
Pyrexia	14.2	8.1
Somnolence	9.3	2.2
Vomiting	9.0	7.0
Pruritus	7.9	3.7
Headache	6.8	4.4
Dizziness (excl. Vertigo)	6.5	2.2
Constipation	4.1	1.1
Confusion	4.7	0.7

The adverse effects listed in Table 11 have been found for all comparator drugs as well.[64-67]
A thorough review of the published comparative studies didn't show any advantage of oxymorphone over the comparator drugs.[69-71;73;74]
One clinical trial showed a significantly higher incidence of vomiting using the IV form of oxymorphone.[73]

DRUG INTERACTIONS:

Table 12: Possible interactions (list not complete) [62-67]

Adverse reactions	**Opana** Oxymorphone HCl	**Opana ER** Oxymorphone HCl	**Dolophine** Methadone HCl	**MS Contin** Morphine	**Oxycontin** Oxycodone HCl	**Duragesic** Fentanyl
CNS depressants	yes	yes	yes	yes	yes	yes
Mixed agonist / antagonists	yes	yes	yes	yes	yes	
Anticholinergics	yes	yes	yes	yes	yes	NA
CYP450	no interactions with CYP450 known	no interactions with CYP450 known	CYP3A4, CYP2B6, and CYP2C19 (CYP2C9 and CYP2D6)	no interactions with CYP450 known	2D6	3A4

PRODUCT AVAILABILITY AND DOSING:
As with any opiate, dosing should be adjusted for each patient individually, taking into account the patient's prior analgesic treatment.[62;63]

Table 13: FDA approved dosing of opioids[62-67]

Trade Name	Strength	Usual Starting Dose	Maximum dosage	Special Instructions
OPANA	tablets: 5 mg 10 mg (containing 5 mg / 10 mg of oxymorphone hydrochloride) *and: injectable*	opioid-naïve patients: 10 to 20 mg by oral administration	may repeat every four to six hours depending on the pain intensity	initiation of therapy with doses higher than 20 mg is not recommended because of potential serious side effects 1hour prior or two hours after eating
OPANA ER	tablets: 5 mg 20 mg 7.5 mg 30 mg 10 mg 40 mg 15 mg	opioid-naïve patients: 5 mg every 12 hrs	in 12-hour-intervals, dosage depending on the pain intensity Titration by increments of 5-10 mg every 12 hrs every 3-7 days	swallow whole 1hour prior or two hours after eating
Dolophine	tablets: 5 mg 10 mg	opioid-naïve patients: 2.5 to 10 mg every 8 to 12 hrs	slow titration to effect	conversion from parenteral to oral methadone or from other chronic opioids is highly variable and depends on baseline morphine as well as every individual
MS Contin	tablets: 15 mg 100mg 30 mg 200mg 60 mg	<60 mg morphine/day: 15 mg twice daily	in 12-hour-intervals, dosage depending on the pain intensity	swallow whole
Oxycontin	tablets: 10 mg 40 mg 15 mg 60 mg 20 mg 80 mg 30 mg 160 mg	opioid-naïve patients: 10 mg every 12 hrs	in 12-hour-intervals, dosage depending on the pain intensity	swallow whole

ISMP SAFETY ALERTS (www.ismp.org):
None.
Tall man lettering, however, is recommended, e.g. OxyMORPHONE to minimize confusion with oxycodone or hydromorphone.[75]

MONITORING:
Respiratory rate, blood pressure, pulse, level of pain, sedation.
UCSF has established processes and mechanisms for the appropriate monitoring of this medication.

Table 14: COST COMPARISONS (April 28, 2008)**:**

Trade Name	Cost	Regimen	Cost/day
Opana			
5 mg	**$1.94**	5 mg PO Q 6 hours	$7.76
10 mg	**$3.52**	10-20 mg PO Q 6 hours	$14.00 - $28.00
Opana ER			
5 mg	**$1.28**	5 mg PO Q 12 hours	$2.56
10 mg	**$2.70**	10 mg PO Q 12 hours	$5.40
20 mg	**$4.35**	20 mg PO Q 12 hours	$8.70
MS Contin			
30 mg	**$0.41**	MS Contin 30 mg PO Q 24 hours	$0.41
60 mg	**$0.73**	MS Contin 60 mg PO Q 24 hours	$0.73
Methadone			
10 mg	**$0.24**	Methadone 20 mg PO Q 24 hours	$0.48
Oxycontin			
10 mg	**$1.22**	Oxycontin 10 mg PO Q 24 hours	$1.22
20 mg	**$2.33**	Oxycontin 20 mg PO Q 24 hours	$2.33
30 mg	**$3.50**	Oxycontin 30 mg PO Q 24 hours	$3.50
40 mg	**$4.12**	Oxycontin 40 mg PO Q 24 hours	$4.12

CONCLUSION AND RECOMMENDATIONS:
- Oxymorphone is an oral therapeutic option approved for the treatment of acute and chronic moderate-to-severe pain after surgery, available in a rapid and delayed onset form as well as in an IV form.[62;63]
- Oxymorphone has a safety and efficacy profile similar to that of other commonly used pure opioids.[76]
- Existing studies are consistent, that the use of oral oxymorphone is as effective and safe as comparator opiates.
  No superiority of oxymorphone regarding efficacy and safety has been observed.[69-71;73;74;76;77]
- The quantity of existing comparative studies is very poor. No studies comparing oral or IV oxymorphone to oral or transdermal fentanyl or oral or IV methadone are available. The three comparative studies used in this review were conducted in different settings and used varying oral and IV formulations.
- Although initially oxymorphone has a rapid onset of action, it appears less effective than morphine with repeat dosing (chronic therapy).[70]

- The adverse effects that have been observed with oxymorphone are similar to those seen with other mu-agonists currently available on the US market. An overall advantage regarding nausea and vomiting wasn't observed.[69-71;73;74;76;77]
- In one study, when administered IV via patient controlled analgesia, oxymorphone caused significantly more nausea and vomiting, but less sedation when compared with morphine.[73] This findings have not been confirmed in more recent studies.[71]
- There are no studies available comparing the abuse potential of oxymorphone compared to other opiates.
- More concerning is the significant influence of food on the absorption of oxymorphone, especially when used as rescue medication.

Further comparative studies targeting potential advantages of oxymorphone over other opioids in the UCSF formulary have to be carried out before considering this opioid for addition to the UCSF formulary.

CHAPTER 2, Example 2

A review of three stand-alone topical thrombins for surgical hemostasis

This part of the PhD thesis has been published under the supervision of Christine M. Cheng, PharmD, UCSF, in Clinical Therapeutics 2009, volume 31, issue 1.[78]

ABSTRACT

Background:

Topical thrombins are active hemostatic agents that can be used to minimize blood loss during surgery. Before 2007, the only topical thrombins available were derived from bovine plasma. Antibody formation to bovine thrombin and/or factor V, with subsequent risk of cross-reactivity with human factor V, and hemorrhagic complications associated with human factor-V deficiencies have been described in case reports of surgeries in which bovine thrombins were used. This risk is now included in the boxed warning section of the bovine thrombin prescribing information.
In 2007 and 2008, 2 new topical thrombins from nonbovine sources received approval for use from the US Food and Drug Administration. The 3 active topical thrombins that are currently marketed are bovine plasma-derived thrombin, human plasma-derived thrombin, and human recombinant thrombin.

Objective:

The purpose of this review was to evaluate the literature on the efficacy and safety of topical thrombins and discuss the pharmacoeconomic considerations associated with their use.

Methods:

Pubmed, Embase, and International Pharmaceutical Abstracts were searched for relevant papers published in English through October 10, 2008, using the terms *thrombin, human recombinant thrombin, bovine thrombin, plasma derived thrombin,* and *topical thrombin.* Manufacturer-provided materials were also reviewed. Abstracts and unpublished data, as well as evaluations of sealants, adhesives, glues, and other hemostats that contain thrombin mixed with fibrinogen and other clotting factors, were excluded.

Results:

Four randomized, double-blind studies involving the active, stand-alone topical thrombins were found. The bovine thrombin involved in these studies was the predecessor to the currently marketed, highly purified bovine formulation. No studies comparing the human products, studies involving the highly purified bovine preparation, or placebo-controlled studies involving bovine thrombin were found. In a Phase III comparison of human recombinant thrombin and bovine thrombin, the percentages of patients who achieved hemostasis within 10 minutes of topical thrombin application were 95.4% and 95.1 %, respectively (95% CI, -3.7 to 5.0).

The incidence of hemostasis within 10 minutes was also similar in a Phase III comparison of human plasma-derived thrombin and bovine thrombin (both, 97.4% [95% CI, 0.96 to 1.05]).
In the study that compared human recombinant and bovine thrombin, the incidence of antiproduct antibody formation was 21.5% (43/200) in the bovine thrombin group and 1.5% (3/198) in the human recombinant thrombin group (P < 0.001); patients with antibodies to bovine thrombin had numerically higher incidences of bleeding or thromboembolic events than did patients without these antibodies (19% vs. 13%; P value not reported).
Human plasma-derived thrombin is available as a frozen sterile solution that must be thawed before application, whereas the human recombinant and bovine plasma-derived products are supplied as unrefrigerated sterile powders that must be reconstituted before use.
The human thrombins are more costly than bovine thrombin on a per-vial basis. The average wholesale prices (US $, 2008) for 5000-IU vials of bovine thrombin and human recombinant thrombin were $87.85 and $103.20, respectively; the average wholesale price for a 4000- to 6000-IU vial of human plasma-derived thrombin was $96.00.

Conclusions:

Topical thrombins vary in the ways in which they are manufactured and their safety profiles, storage requirements, and costs. Human recombinant thrombin and human plasma-derived thrombin have each been shown to have hemostatic efficacy comparable to that of bovine thrombin. Bovine thrombin carries the risk of formation of cross-reactive antibodies to bovine thrombin, factor V, and other impurities that may be present in these formulations.
Immunogenicity data for the currently marketed, highly purified bovine thrombin relative to older formulations of bovine thrombin could not be found. Whether the potential safety advantage justifies the added cost of the human products remains to be established.

INTRODUCTION

Topical thrombin is a hemostatic agent that is commonly used to facilitate hemostasis in a variety of surgical settings.[79] Topical thrombin may be applied directly to the wound via topical spray, used in conjunction with absorbable gelatin or collagen sponges, or included as a component of wound dressings and fibrin and platelet sealants.[79] It has been conservatively estimated that topical thrombin is used in >1 million surgical procedures and costs $250 million annually in the United States.[80]

The first topical thrombin* to be approved by the US Food and Drug Administration (FDA) for use in the United States emerged in 1943. Two additional products were approved decades later (one in 1986** the other in 1995***).[81] All of these products were derived from bovine plasma through different purification processes. Historically, bovine-derived thrombins have been associated with rare reports of hemostatic abnormalities, ranging from asymptomatic laboratory changes (e.g., prolonged prothrombin time [PT] and partial thromboplastin time [PTT]) to severe refractory bleeding and thrombosis.[80] These events may be related to the development of antibodies to bovine factor V and other bovine protein contaminants present in the thrombin preparations. In some cases, these antibodies cross-reacted with homologous human factors, resulting in factor-V deficiency and impaired hemostasis.[80;82;83] Manufacturers of bovine thrombins have responded to immunogenicity issues by preparing bovine products of increasing purity. The currently marketed formulation of bovine plasma-derived thrombin (Thrombin-JMI), approved for use in the United States in January 2008, represents the purest bovine thrombin yet, with bovine factor-Va levels below the limit of detection by semi quantitative Western blot analysis.[82;84]

Recently, two topical thrombin products from nonbovine sources became available. Human plasma-derived thrombin was approved for use in the United States in August 2007+, and human recombinant thrombin was approved in January 2008§. The human thrombins are not associated with the risk of antibovine factor-V development or potential factor-V antibody formation.[81]

The FDA-approved indication for each of the available topical thrombin products is identical. They are used as adjunctive hemostatic agents whenever oozing blood or minor bleeding from capillaries and small venules is accessible and not manageable by conventional methods (e.g., pressure, suture, ligature, cautery).[84-86] They may be applied directly to the bleeding site or in conjunction with an absorbable gelatin sponge.[84-86]

This review summarizes the published literature on the efficacy and tolerability of the 3 commercially available stand-alone, single-ingredient, topical thrombin products available in the United States and discusses pharmacoeconomic considerations associated with these products.

* Trademark: Thrombostat' (Parke-Davis, Morns Plains, New Jersey)
** Trademark: Thrombogen' (Ethicon Inc., a Johnson & Johnson company, Somerville, New Jersey).
*** Trademark: Thrombin-JMI (King Pharmaceuticals, Inc., Bristol, Tennessee).
\+ Trademark: Evithrom (Johnson & Johnson Wound Management, Somerville, New Jersey).
§ Trademark: Recothrom (ZymoGenetics Inc., Seattle, Washington)

METHODS

Pubmed, Embase, and International Pharmaceutical Abstracts were searched for clinical trials and review articles on the use of active, stand-alone, topical thrombin products that were published in English through October 10, 2008. The search was conducted using the terms *thrombin, human recombinant thrombin, bovine thrombin, plasma derived thrombin,* and *topical thrombin.* References in the retrieved articles were also reviewed for additional relevant articles. The manufacturer's prescribing information and formulary dossiers for the 3 products were also obtained.[84-86]
Abstracts and unpublished information were excluded from analysis. Evaluations of sealants, adhesives, glues, and other hemostats that contain thrombin mixed with fibrinogen and other clotting factors were excluded from the review.

RESULTS

Product Description

Topical thrombins vary in the ways in which they are manufactured and their safety profiles, storage requirements, and costs. Bovine thrombin is produced by extracting prothrombin from bovine plasma. After activation to thrombin, the product undergoes a chromatographic purification process that includes ion exchange and viral filtration.[82;84] The added step of viral filtration reduces bovine factor-Va levels to <92 ng/mL, which is below the level of detection by semi quantitative Western blot analysis.[82] The previous formulation of Thrombin-JMI, which underwent chromatographic purification, had a factor-Va concentration of <200 ng/mL.[87]
Human thrombin is derived from human plasma from FDA-licensed plasmapheresis centers in the United States.[85] Plasma is screened and tested for hepatitis B surface antigen; human immunodeficiency virus type-I and type-2 antibodies; hepatitis A, B, and C viruses; and parvovirus B19 according to FDA regulations. Prothrombin is extracted, activated, and then purified by solvent-detergent treatment and nanofiltration to inactivate and remove any viruses. The purified solution is then mixed with calcium chloride, sterile filtered, and frozen.[85]
Human recombinant thrombin is produced via recombinant DNA technology from genetically modified Chinese hamster ovary cells that produce human thrombin precursors.[86] Enzymes derived from snake venom are used to activate the precursors to human thrombin. The thrombin is then purified in a chromatographic process that includes solvent-detergent treatment and nanofiltration. Human recombinant thrombin is identical in amino-acid sequence to naturally occurring human thrombin. Other characteristics of these thrombin products are shown in Table 15.[84-86]

Table 15: Commercially available topical thrombin products in the United States [84-86]

Generic	Brand (manufacturer)	FDA approval date	How supplied	Final concentration	Storage
topical bovine thrombin	Thrombin-JMI® (Jones Pharma)	03/14/2008 (new purified formula) first approval: 1995	Sterile powder with diluent Pump spray kit (5, 10, 20 mL) Syringe spray kit (10, 20 mL) Epistaxis kit (5 mL) Vial 1 mL (ready-to-use) Vial 5 mL Vial 10 mL Vial 20 mL	1000 IU/mL	Unopened vials at 2 to 25°C 1 mL ready-to-use vial at 2-8°C Reconstituted solution at 2 to 8°C for up to 24 hours or at room temperature for up to 8 hours
topical human thrombin	Evithrom® (J&J Wound Management) Also an ingredient in Evicel Fibrin Sealant®	08/25/2007	Frozen sterile solution Vial 2mL Vial 5mL Vial 20mL	800-1200 IU/mL	Frozen at 18°C for up to 2 years Refrigerated at 2 to 8°C for up to 30 days Thawed at room temperature for up to 24 hours
topical recombinant thrombin	Recothrom® (ZymoGenetics)	01/17/2008	Sterile powder with diluent Vial 5mL	1000 IU/mL	Unopened vials at 2 to 25°C Reconstituted solution at 2 to 25°C for up to 24 hours

Pharmacology

Thrombin (activated factor II) is a serine protease that has multiple functions in the coagulation cascade. It converts fibrinogen into fibrin monomers, which cross-link to form a stable fibrin clot.[80] Thrombin also activates clotting factors V, VIII, XI, and XIII and promotes platelet aggregation and adherence in wounds.[81] Inhibition of thrombin activity by antithrombin III and protein C-mediated inhibition of factors V and VIII occur rapidly; hence, the thrombin effects are local and limited, and intravascular coagulation is avoided.[80;81] Thrombin has also been shown to affect a multitude of other cell types, including fibroblasts, cardiomyocytes, keratinocytes, and monocytes, as part of the hemostatic and inflammatory response to vascular tissue injury. The multifunctional roles of thrombin are actively being explored and researched.[80;88]

Pharmacokinetics

No formal pharmacokinetic studies on topical thrombin products were identified in the literature search. Topically applied thrombin is expected to have only local effects.[84-86]

Product-Specific Risks

The prescribing information for topical bovine thrombin includes the following boxed warning: "The use of topical bovine thrombin preparations has occasionally been associated with abnormalities in hemostasis ranging from asymptomatic alterations in laboratory determinations, such as prolonged PT and PTT, to severe bleeding or thrombosis which rarely have been fatal.

These hemostatic effects appear to be related to the formation of antibodies against bovine thrombin and/or factor V, which in some cases may cross-react with human factor V, potentially resulting in factor V deficiency. Repeated clinical applications of topical bovine thrombin increase the likelihood that antibodies against thrombin and/or factor V may be formed. Consultation with an expert in coagulation disorders is recommended if a patient exhibits abnormal coagulation laboratory values, abnormal bleeding, or abnormal thrombosis following the use of topical thrombin. Any interventions should consider the immunologic basis of this condition. Patients with antibodies to bovine thrombin preparations should not be re-exposed to these products."[84]

Antibodies to bovine factor V may cross-react with human factor V, leading to human factor-V deficiency that may be severe enough to cause excessive bleeding.[80] Paradoxical cases of thrombosis have also been documented in patients who developed factor-V inhibitors following bovine thrombin treatment.[89] Although many anecdotal reports of adverse reactions to topical bovine thrombins have been published, the true frequency of these events, in relation to the worldwide utilization of topical thrombins, is not known.[80;89-91]

The association between antibody development and coagulopathies following bovine thrombin use has been established through case reports, rather than rigorous clinical trials. For example, the frequency of antibody development ranges from 10% to 95% in the published literature, and the cases are difficult to compare because of differences in the types of surgery, types of bovine antibodies being measured (thrombin, factor V, or other clotting factors), bovine thrombin preparations used, antibody detection techniques, and other patient factors.[81;90-94] The rate of serious bleeding among patients with bovine thrombin-induced factor-V antibodies was 33 % according to a review of 58 cases, 6% of which were fatal.[89] In addition, cases of coagulopathies that may be associated with topical bovine thrombins may be unrecognized and unreported.[89]

Despite the FDA recommendation that patients with these antibodies not be re-exposed to topical bovine preparations, there is presently no FDA-approved laboratory test available to screen patients for the presence of antibodies to bovine thrombin.[80] Attempting to identify patients previously exposed to bovine thrombin is often difficult to achieve by reviewing medical records because thrombin use may not be documented consistently in the patient's hospital chart.[89]

Symptoms of factor V deficiency include prolonged PT and activated PTT, which may occur within 7 to 14 days after bovine thrombin exposure and persists for an average of 2 months.[87;89] Excessive bleeding that is refractory to vitamin K and fresh frozen plasma is usually indicative of factor-V activity that is <30% of normal.[87]

Treatment of antibody-induced factor-V deficiency is guided by symptom severity. Asymptomatic laboratory abnormalities require no specific treatment but should be monitored closely. Immunosuppression with corticosteroids and combination chemotherapy agents, high-dose intravenous immune globulins, plasmapheresis, and plasma and platelet transfusions have been effective in managing hemorrhagic complications.[89;92;95]

Although human plasma-derived thrombin avoids the issue of cross-immunogenicity, it does carry the potential to transmit infections from infected plasma donors. Screening plasma donors for exposure to certain infectious agents, such as viruses and Creutzfeldt-Jakob disease (CJD), and testing for infectious agents reduces but does not eliminate the risk of transmitting disease, including unknown infectious agents. Patients should be aware of the risks and benefits of human plasma-derived thrombin use before undergoing treatment. To date, no cases of CJD or viral seroconversion have been reported.[85]

Human recombinant thrombin is the only plasma-free thrombin product available. It minimizes the risks of immunogenic cross-reactivity and infection transmission from human plasma donors.[81]

Therapeutic Efficacy

Four randomized, double-blind studies on the efficacy and safety of active, stand-alone topical thrombins were identified in the literature search.[96-99] One was a placebo-controlled study of human recombinant thrombin,[97] 2 studies compared the efficacy and safety of human recombinant thrombin and bovine thrombin,[96;98] and 1 study compared the efficacy and safety of human plasma-derived thrombin and bovine thrombin[99]. All of these studies were conducted between April 2004 and July 2006. Despite the use of topical bovine thrombins for decades before they were approved by the FDA, no published studies evaluating the efficacy of stand-alone topical bovine thrombin relative to placebo were identified in the literature search.

In a Phase II, double-blind, placebo-controlled, efficacy and safety analysis of human recombinant thrombin conducted by Chapman et al.,[97] 130 adults undergoing arteriovenous (AV) graft formation for hemodialysis, major hepatic resection, peripheral arterial bypass (PAB) surgery, or spinal surgery were randomized to receive a single application of either human recombinant thrombin (1000 IU/mL) or placebo. Patients with hypersensitivity to thrombin or other coagulation factors were excluded. The treatments were added to either Gelfoam® (Pharmacia, Kalamazoo, Michigan) or Surgifoam® (Johnson & Johnson, Somerville, New Jersey) gelatin surgical sponges before application. Time to hemostasis (TTH) was measured for a maximum of 10 minutes, after which human recombinant thrombin could be used as rescue therapy if needed. Ten percent (9/93) of the bleeding sites in the thrombin-treated group and 20% (18/90) of those in the placebo group required rescue therapy. A hazard ratio of 1.3 was reported for the comparison of TTH for thrombin versus placebo, although the authors state that the study was not powered to detect significant differences between the 2 groups or designed to test any formal statistical hypotheses. In addition, the results were not stratified by surgery type or type of sponge used; thus, the wound site and severity of bleeding, as well as any differences in the intrinsic properties of the gelatin sponges, were not addressed.

Chapman et al.[96] also conducted a Phase III non-inferiority evaluation, in which the efficacy and tolerability of human recombinant thrombin (1000 IU/mL) was compared with bovine thrombin (1000 IU/mL) in 401 adults undergoing hepatic resection, spinal surgery, PAB surgery, or AV graft formation. Patients with known sensitivity to bovine materials were excluded from the study. Both treatments were applied with an absorbable gelatin sponge (Gelfoam® for spinal surgeries, Surgifoam® for nonspinal surgeries). Overall, the TTH within 10 minutes after a single application of study drug was 95.1 % in the bovine thrombin group and 95.4% in the human recombinant thrombin group (95% CI, -3.7 to 5.0). Because this study did not include a placebo arm, no conclusions can be drawn about the efficacy of either human recombinant thrombin or bovine thrombin relative to placebo.

In a separate subanalysis led by Weaver et al.[98] data from 144 vascular surgery patients (PAB or AV graft formation) who had participated in the Phase III human recombinant thrombin comparative trial were further evaluated. This study found that, among the 88 patients who underwent PAB surgery, 55% (45/82) of the bleeding sites treated with human recombinant thrombin and 39% (32/83) of those treated with bovine thrombin achieved hemostasis within 3 minutes (P = 0.046). The clinical significance of this finding is not known and has yet to be reproduced in other studies.

Doria et al.[99] conducted a randomized, double-blind study in which human plasma-derived thrombin (800-1200 IU/mL) was compared with bovine thrombin (1000 IU/mL) in 305 adults undergoing elective cardiovascular, spine, and general or posttraumatic surgery. Patients with known antibodies to bovine thrombin preparations were excluded from the study. Treatments were applied using a gelatin sponge (Surgifoam®), and hemostasis was assessed at 3, 6, and 10 minutes after treatment. The treatments were considered equivalent if the 95% CIs for both treatments were between 0.8 and 1.25. When all surgical types were combined, 97.4% of the human plasma-derived thrombin recipients and 97.4% of the bovine thrombin recipients experienced hemostasis within 10 minutes (95% CI, 0.96 - 1.05). At 6 minutes, the success rate for human plasma-derived thrombin was 94.8% compared with 92.8% for bovine thrombin (95% CI, 0.96 - 1.09); at 3 minutes, the success rates were 73.2% and 72.4%, respectively (95% CI, 0.88 - 1.16). The proportion of patients achieving hemostasis was also equivalent at each time point when analyzed by surgery type. Again, this study lacked a placebo group, so no conclusions could be drawn about the absolute benefit of thrombin compared with conventional care.

Based on the results of these studies, the efficacy of the human and bovine thrombin products seems to be comparable; however, several inherent limitations should be noted. Differences in surgical technique, hemostasis assessment, patient-specific bleeding risk, type and size of sponge used, thrombin application technique, and use of preoperative hemostatics may have influenced the TTH.

Perhaps even more important, the only study to include a placebo arm was not designed to detect differences in efficacy; thus, the absolute utility of topical thrombins compared with conventional techniques to minimize intraoperative bleeding remains unclear. Furthermore, published comparative studies between human plasma-derived thrombin and human recombinant thrombin could not be found, and it should be noted that the comparator bovine product used in these studies was an older version of Thrombin-JMI than the one currently being marketed; no comparative studies involving the current formulation were identified in the literature search.

Adverse Effects

In the Phase II, placebo-controlled study of human recombinant thrombin in 130 adults conducted by Chapman et al.,[97] patients exposed to human recombinant thrombin (n = 88) experienced a numerically higher incidence of mild to moderate nausea (26% vs. 45%), constipation (12% vs. 27%), insomnia (5% vs. 19%), and vomiting (2% vs. 13%) than did patients in the placebo group (n = 42). Whether these differences were statistically significant is not known because no formal statistical tests were performed in this study, and there may not have been enough participants to detect significant differences between the treatment groups.[97] These results may have been confounded by the number of patients who received rescue therapy with human recombinant thrombin, who also may have had more extensive bleeding or more complicated surgeries. Changes in laboratory and coagulation parameters were similar for the groups (incidences not reported). Two patients (1 in the thrombin group and 1 in the placebo group) developed antibodies to the human recombinant product; however, these antibodies had no effect on extrinsic or endogenous thrombin activity and were not associated with any bleeding complications. It is unclear why the patient in the placebo group developed these antibodies.[97]

In the Phase III study conducted by Chapman et al.[96] the incidences of adverse events and abnormal laboratory parameters were similar for patients treated with human recombinant thrombin and those treated with bovine thrombin. The most common adverse events included nonspecific incision-site complications (63% in both groups), nausea and vomiting (33% vs. 40% in the human recombinant thrombin and bovine thrombin groups, respectively), procedural pain (29% vs. 34%), nonspecific cardiac problems (20% vs. 18%), and infection (13% vs. 15%). The human recombinant thrombin group had a significantly lower incidence of positive antibodies than the bovine thrombin group (1.5% [3/198] vs. 21.5% [43/200], respectively; $P < 0.001$); 1.5% (3/200) of the patients in the human recombinant thrombin group and 5% (10/198) of those in the bovine thrombin group already had antibodies to the administered product at baseline. Among these patients, 80% (8/10) of the bovine thrombin recipients experienced at least a 1-unit increase in antibody titer after treatment, whereas none of the human recombinant thrombin recipients experienced such increases.

The TTH was not affected by the presence of baseline antiproduct antibodies in either treatment group, and the presence of anti-recombinant antibodies did not have a neutralizing effect on native human thrombin activity. In a 1-month post hoc analysis, patients with antibovine thrombin antibodies had numerically higher incidences of undefined bleeding and thromboembolic events (19% vs. 13%), hypersensitivity events (18% vs. 16%), and elevated levels of activated PTT (33 % vs. 14%) compared with patients without these antibodies. None of the patients with antibodies to human recombinant thrombin experienced these adverse outcomes.[98] The incidences of prolonged PT and international normalized ratio (INR) abnormalities were similar in patients with and without bovine antibodies (data not reported). The incidences of specific antibodies against bovine and human factor V were not reported. The FDA review of this study noted that it was unclear whether chance alone could have accounted for the rate of bleeding adverse events among subjects with positive antibovine antibodies, because the study was not designed to evaluate differences in immunogenicity.[100]

In a Phase III study comparing human plasma-derived thrombin and bovine thrombin in 305 patients, conducted by Doria et al. the incidence of laboratory abnormalities was 95% in the human plasma-derived thrombin group and 98% in the bovine thrombin group; however, the incidences of specific hematologic abnormalities, including elevated INR and prolonged PT and PTT, were not reported.[99] Of the 248 patients included in the antibody assessment, the rate of antibody development was 3% (4/122) in the human plasma-derived thrombin group and 13% (16/126) in the bovine thrombin group ($P < 0.01$). The incidence of antibovine factor V/Va antibody development was also significantly higher in patients treated with bovine thrombin (10% [12/126]) than in those treated with human plasma-derived thrombin (2% [2/122]; $P = 0.01$). The 2 patients who developed antibovine antibodies in the human plasma-derived thrombin group had been exposed to bovine thrombin before study enrollment. None of the patients in this study developed antihuman factor-V antibodies; viral serologies were not monitored.

Contraindications

All thrombin products are contraindicated for injection into the circulatory system because of the risk of thrombosis, and they should not be used to treat severe or brisk arterial bleeding. Bovine thrombin should not be administered to patients with hypersensitivity to any of its components or to materials of bovine origin.[84] The use of human plasma-derived thrombin is contraindicated in patients with a history of severe systemic reactions or anaphylaxis to human blood products.[85] Patients with known hypersensitivity to hamster proteins, snake proteins, or any component of human recombinant thrombin should not be treated with this agent due to the risk of allergic reaction.[86]

Drug Interactions

There are no known drug interactions with the topical thrombins.[84-86]

Dosing and Administration

All topical thrombin vials and spray kits are intended for single use only. The amount of thrombin required for a particular surgery depends on the size of the bleeding site and method of application.[84-86] Specific dosing guidelines for the individual thrombins could not be found. Topical thrombins should be applied to the surface of bleeding tissue, either directly to the site or in conjunction with an absorbable gelatin sponge, according to the manufacturer's instructions.[84-86]
The clinical studies involving human plasma-derived thrombin used volumes of up to 10 mL.[85]
The amounts of topical thrombins used in the other studies were not reported.

Pharmacoeconomic Considerations

The average wholesale prices of the topical thrombins are listed in Table 16.[86;101;102]

Table 16: Average wholesale price of topical thrombin preparations (US $, 2008)[86;101;102]

Product	Vial size	Price	Cost/IU
Bovine topical thrombin	5,000 IU vial	$87.85	$0.017
(Thrombin JMI)	20,000 IU vial	$323.47	$0.016
	20,000 IU vial with spray pump	$339.68	$0.017
	20,000 IU vial with syringe & spray tip	$339.66	$0.017
Human plasma derived	1,600-2,400 IU vial (2 mL)	$67.00	$0.028 - 0.042
topical thrombin	4,000-6,000 IU vial (5 mL)	$96.00	$0.016 - 0.024
(Evithrom)	16,000 - 24,000 IU vial (20 mL)	$375.00	$0.016 - 0.023
Recombinant topical	5,000 IU vial	$103.20	$0.020
thrombin (Recothrom)	20,000 IU vial	$412.80	$0.021
	20,000 IU with spray kit	$434.40	$0.022

Bovine topical thrombin costs less than the human products on a per-vial basis.[101]
Whether the potential safety advantage of the human thrombins justifies their added expense is unknown and depends on a variety of factors.
First, the incidence of factor-Va antibody formation with the currently marketed, highly purified formulation of bovine thrombin is unknown; whether this preparation is less immunogenic, particularly for patients previously exposed to bovine products of lesser purity, has yet to be determined.
The minimum concentration of bovine factor V needed to induce an immunogenic reaction has not been established. Although no immunogenicity data are available for the current formulation of bovine thrombin, this formulation carries the same black-box warning as previous thrombins of lesser purity that were derived from bovine sources.
Differences in storage requirements for the 3 products should also be considered when selecting a topical thrombin. Human plasma-derived thrombin is supplied as a frozen sterile solution that may be stored frozen for up to 2 years or refrigerated for up to 30 days.[85] Once refrigerated, the solution should not be refrozen. The thawed solution can be stored at room temperature for up to 24 hours before use. Once thawed, the solution should not be refrigerated; any thawed solution that is unused within 24 hours must be discarded.
In contrast, bovine thrombin and human recombinant thrombin are supplied as sterile powders that are stored at room temperature. After reconstitution, bovine thrombin can be refrigerated for up to 24 hours or stored at room temperature for up to 8 hours before use. Reconstituted solutions of human recombinant thrombin can be stored at room temperature for up to 24 hours before use.[84;86]
These differences in storage requirements may be important when considering strategies to minimize potential waste from unused thawed or reconstituted drug.
To date, no formal pharmacoeconomic analyses for the topical thrombins have been published.

DISCUSSION

Topical thrombins vary in the ways in which they are manufactured and their safety profiles, storage requirements, and costs. No immunogenicity data are available for the currently marketed bovine thrombin, and no head-to-head comparison studies have been conducted on the current formulation. The clinical significance of manufacturing changes that have progressively reduced the level of bovine factor-V contaminants in bovine thrombin preparations has yet to be determined. The safety of repeated applications of human plasma-derived thrombin or human recombinant thrombin is also unknown. In addition, the lack of rigorous placebo-controlled studies of the topical thrombins also raises the question of their advantages over conventional techniques to minimize blood loss.

The number of randomized, controlled studies assessing the efficacy of the stand-alone topical thrombins is surprisingly sparse, given that topical thrombins have been in use for >60 years. It should be noted, however, that we excluded evaluations of sealants, adhesives, and glues, which often incorporate a mixture of platelets, thrombin, fibrinogen, and other clotting factors. Nevertheless, the impact of topical thrombin use on patient or surgical outcomes has yet to be clearly established.[80] Mechanisms to document and track patient exposure to thrombins are also needed to determine the potential risk of developing antibovine, antibody-mediated coagulopathies in patients for whom use of a topical bovine thrombin is anticipated.

CONCLUSIONS

Three topical thrombins are currently marketed in the United States: bovine plasma-derived, human plasma-derived, and human recombinant thrombin. The bovine thrombin is a highly purified preparation, although it still carries a boxed warning that describes the risk of immunogenicity reactions associated with formation of potentially cross-reactive antibodies to bovine thrombin, factor V, and other impurities that may be present in the bovine preparation. More experience with these products is needed to determine whether any efficacy, safety, or economic differences exist between them.

Since the IOM report “To Err is Human”, health-care institutions must proactively pursue medication safety, assessing institution-specific data and ensuring the quality of drug therapy.[7] The previous chapter provided examples of evidence-based literature reviews for the consideration of formulary additions. In the following chapters, methods for the assessment of institution-specific medication use safety are discussed.

Myers et al. recommend an interdisciplinary approach to medication safety:

1. Establishing a common agreement that there is a problem.
2. Establishing a common aim (a shared vision) to improve.
3. Identifying requisite elements of safety.
4. Redesigning medication use, if necessary.
5. Establishing ongoing surveillance.
6. Establishing ongoing dialogue on the subject
   (educational conference, opinion survey, collaborative activities).[103;104]

While the following organizations provide guidance for medication safety activities in individual healthcare institutions, it is unknown, which method is the most efficient and effective.

[last accessed: February 27, 2011]

- Institute for Safe Mediation Practices ISMP
  www.ismp.org
- Institute for Health Care Improvement IHI
  www.ihi.org
  (see also: "The 100'000 lives campaign")
- National Health Service United Kingdom NHS
  www.nhs.co.uk
- The Joint Commission
  www.jointcommission.org
- Agency for Healthcare Research and Quality
  www.ahrq.org
- U.S. Veterans Affairs National Center for Patient Safety
  www.patientsafety.gov
- The Leapfrog Group
  www.leapfroggroup.org
- The National Quality Forum
  www.qualityforum.org
- Dennis Quaid Foundation (e.g., "Chasing Zero")
  dsc.discovery.com/videos/chasing-zero-part-1.html
- The World Health Organization
  www.who.org
  (see also: www.high5s.org)
- The American Society of Health-System Pharmacists
  www.ashp.org
  (see also: "The 2015 Health System Pharmacy Initiative" www.ashp.org/2015)

In the light of limited resources as for example in Swiss hospital pharmacies with only 0.76 FTEs per 100 beds, the question of an optimal method for medication safety assessment shall be addressed in chapter 3.

CHAPTER 3

Medication safety assessment methods:

How can institutions efficiently address drug-related problems?

This chapter has been published in The American Journal of Health System Pharmacy 2011, Volume 68, Issue 3, 227-240.[34]

ABSTRACT

Background

Health care institutions continuously assess the safety of medication use through active monitoring, identification of important drug-related problems (DRPs) and development of remediation strategies. Recommended methods from organizations, such as the Institute for Safe Medication Practice, include incident reporting (IR), direct observation (OB), chart review (CH) and trigger tool analysis (TR). However, the optimal method for identifying DRPs is unknown. The aim of this manuscript is to review the accuracy, efficiency and efficacy of these 4 commonly recommended medication safety methodologies.

Methods

Pubmed, Embase and Scopus databases were systematically searched for any comparative study in which at least 2 of the 4 chosen methodologies (IR, OB, CH and TR) were compared to one another.

Any study which compared 2 or more methodologies for quantitative accuracy, adequacy for the assessment of medication errors and adverse drug events, efficiency (effort and cost) and efficacy and also provided numerical data were included in the analysis.

Results

Twenty-eight studies were included in this review.

OB identified the greatest number of DRP reports, while IR identified the least. However, IR generally showed a higher specificity compared to the other methods and most effectively captured severe DRPs. In contrast, the sensitivity of IR was lower when compared to TR. Finally, while TR was the least labor-intensive of the 4 methodologies, IR appears to be the least expensive, however, only when linked with concomitant automated reporting systems and targeted follow-up.

Conclusion

All four assessment techniques have different strengths and weaknesses. In addition, overlap between different methods in identifying DRPs is minimal. While TR appears to be the most effective and labor-efficient method, IR best identifies high severity DRPs. Consequently, the review of the use of combination methodologies, such as the TR with IR, is strongly recommended for optimal identification of DRPs.

INTRODUCTION

The health-related and economic burden associated with drug-related problems (DRPs), including adverse drug event (ADEs), adverse drug reactions (ADRs) and medication errors (MEs), has resulted in requirements to ensure improvement of medication safety.[2;7;105] In the state of California, Senate Bill 1875 (SB1875) requires health care institutions to implement a formal plan to reduce drug-related problems as a condition of licensure.[106]

Certain medications commonly referred to as "high-risk" or "high-alert" medications carry a high risk of patient harm if they are misused.[107] The 2008 Joint Commission National Patient Safety Goals require that health care institutions improve the safety of medication use, particularly for certain high risk drugs.[108]

The Institute for Healthcare Improvement's "5 Million Live Campaign" similarly focuses upon prevention of harm associated with high-alert medications.[109] Finally the United States Pharmacopeia and the Institute for Safe Medication Practices (ISMP) have identified those high risk drugs requiring medication use evaluation.[110]

Detection and quantification of DRPs is critical to the identification of underlying causes as well as the creation of remedial action plans.[111;112] The Institute for Healthcare Improvement (IHI)[35], the Institute for Safe Medication Practices (ISMP)[113] and the Joint Commission[108] recommend various methods for medication safety assessment. However, the optimal methodology(ies) for an efficient identification of DRPs in an individual institution has not been identified so far in the published literature. The aim of this review is to characterize and compare the accuracy, efficiency and efficacy of commonly used medication safety methodologies in proactive medication safety assessment.

METHODS

Identification of common approaches to identifying drug-related problems

A literature search was conducted to identify common approaches for identifying DRPs within health systems. The search included the timeframe from January 2000 - October 2009. This timeframe was chosen because of the fundamental changes in drug safety awareness since the publication of the Institute of Medicines' (IOM) report "To err is human"[7], as well as the growing deployment of information technology in healthcare institutions.

Books addressing medication safety issues and indexed in the library database of the University of California system[2;7;105;113-118] as well as recommendations, guidelines and position papers published by IHI[35], ISMP[119], and the Joint Commission[108] were reviewed.

While up to 12 methods used in the assessment of medication safety were identified, we specifically focused upon the 4 most commonly recommended methods (incident report review (IR), chart review (CH), direct observation (OB), and trigger tool (TR)), all of which are widely used at UCSF.

Definitions

The term “drug-related problem” was adopted from the publication of van Mil et al. to encompass all medication-related events.[120] The term includes adverse drug events (ADEs) consisting of adverse drug reactions (ADRs) and medication errors (MEs). It also includes processes (causes) and outcomes (effects) and is not limited to events causing harm.[120]

IR is defined as voluntary reporting of incidents by health care personnel and/or patients and parents. Reporting can either be executed by paper form, email, fax, telephone or via an interactive computer-based mechanism.[113]

OB refers to a wide range of direct, real-time observation techniques of all aspects of the medication use process.[121;122]

CH encompasses concurrent or retrospective medical record review, including, but not limited to, medical records, discharge summaries, pharmacy databases and/or laboratory data.[105;123]

TR consists of a targeted medical record review, either manually or automatically (computer alerts, coded medical records) executed.[105;111]

Identification of studies comparing two or more methods of identifying drug-related problems

An additional systematic review of the literature was conducted including any study that directly compared the selected methodologies (IR, CH, OB and TR) to detect DRPs. Two authors independently reviewed and categorized the studies.

All 4 tools were assessed with respect to:

1) quantification of DRPs (quantity of DRPs identified),

2) accuracy (ability to identify medication errors and adverse drug events),

3) efficiency (effort and cost) and efficacy (ability to identify DRPs).

In addition, the various methodologies were compared with respect to: the severity and type of DRPs, the interprofessional differences in reporting, and the specific component of the medication use process in which the DRP was identified.

Literature search:

The evaluation was based on a systematic literature review of Pubmed, Embase and Scopus databases. In order to search for comparative studies, the free text terms (drug therapy OR drug-related problem OR medication error OR medication errors OR medication safety OR adverse drug event OR adverse drug reaction OR adverse effect OR high risk drug OR high alert drug) AND (assessment OR evaluation OR review OR screening OR surveillance OR strategy) were combined with each of the following permutations on the different methods:

‘

Set 1: (incident OR voluntary) AND (chart review OR chart reviewed)

Set 2: (incident OR voluntary) AND (direct observation OR observer)

Set 3: (incident OR voluntary) AND (trigger OR indicator)

Set 4: (chart review OR chart reviewed) AND (direct observation OR observer)

Set 5: (chart review OR chart reviewed) AND (trigger OR indicator)

Set 6: (direct observation OR observer) AND (trigger OR indicator).

No time or language restrictions were applied.

After screening of the abstracts, all potentially relevant full-text publications were evaluated. A “related articles” search was run against those articles that were considered relevant. References of the retrieved articles were also reviewed for additional relevant articles.

Study categorization

Studies were included if they reported original, comparative, numeric data on at least 2 of the 4 methods.

Studies were excluded

- if the primary objective of the study did not include comparison of at least 2 of the four medication safety assessment methods,
- if the respective methods were studied during different time periods (unless results were adjusted for this difference), or
- if individual numeric results for the methods assessed were not reported.

Two authors independently reviewed and categorized the studies according to (1) whether the study met criteria for inclusion and (2) the types of methods being compared. Disagreements were resolved via consensus. In some cases, the method described in an article differed from the method categorization determined for this review. As an example, if the method assessing DRPs was identified in the primary reference as CH, but was determined to be a targeted study using specific indicators to identify DRPs, it was included in this review as TR.

No other adjustments or recategorizations were undertaken.

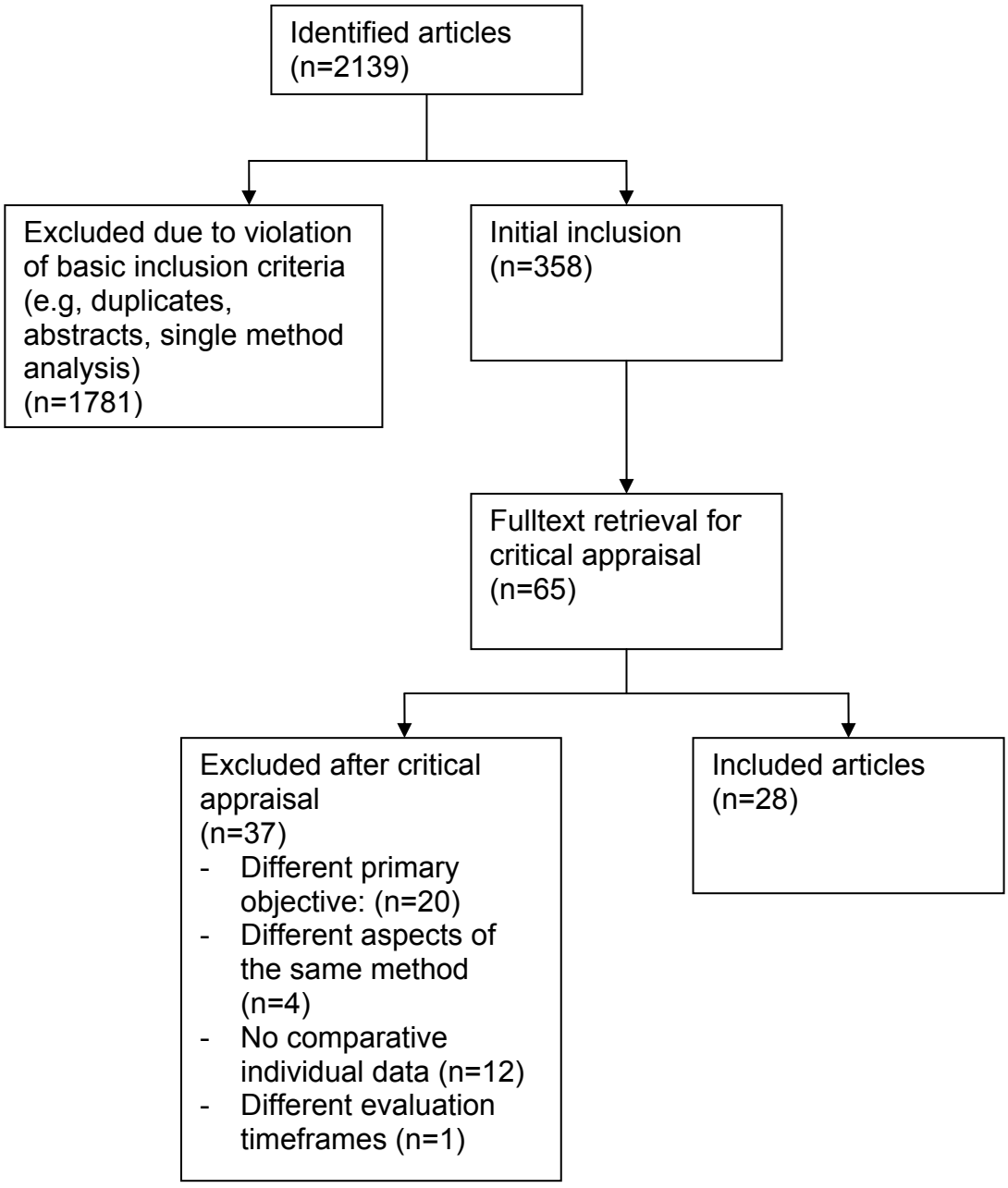
Data extraction:

The following categories were evaluated and entered into an Excel spread-sheet: reference (author, year of publication, origin of the study), setting, methods, original outcome measures, and quantitative results. Accuracy of the different methods was evaluated for positive predictive value PPV, sensitivity, specificity, number of false negatives, and/or number of false positives and interrater agreement; resource utilization was reflected in time effort, and/or cost). Additional data included severity and type of DRPs, identification of the health care provider reporting, and medication use processes associated with the specific DRP.

RESULTS

Our literature review (see figure 1) identified 65 comparative studies involving at least 2 of the 4 medication safety assessment methods. Twenty studies were excluded because comparative data was not provided regarding the medication safety assessment methods. Four studies were excluded because they were determined to have compared different approaches to the same method. Twelve studies did not report comparative data or did not distinguish the results for the individual methods. One study was excluded because different time frames were used for the individual methods to collect DRP data. The remaining 28 studies were included for review. These studies are displayed in Table 17.

Figure 1: Overview of in- and exclusion of articles



Twenty-two of the included 28 publications compared 2 of the 4 methodologies. Six publications compared 3 methods. No publication compared all 4 methodologies.
Twenty-nine percent of the studies evaluated IR, 24% CH, 24% TR and only 9% OB.

Comparative data was inconsistently presented. As an example, the denominator used for reporting detected DRPs varied from total number of DRPs to total number of opportunities for a DRP. The rate of reported DRP also varied with respect to rate per number of beds, number of patients or number of patient days.

Quantification of DRPs

In review of the 4 methodologies, IR was consistently least likely to identify DRPs.
Thirteen studies compared IR to CH.[36;124-135] Chart review consistently yielded more event reports than IR. However, targeted encouragement of providers to report IRs yielded higher rates of IRs.[125;132;135]
In contrast, OB yielded the greatest number of DRP reports in most comparative studies, up to 400 times reported DRPs when compared with IR, TR or CH.[5;124;126;136-138]
Five studies directly compared CH to TR. Two studies reported a higher rate of DRPs using TR, while 3 documented the opposite.[127-129;139;140] The number of DRPs detected by TR compared to CH was directly related to the specificity of the applied triggers; the specificity of the triggers varied from 19.6% to 76%.[128;129;139]
Overlap in the identification of DRPs with the respective methods was rarely observed. As an example, the reported agreement between IR and TR was found to be only 0.5% - 10%.[127;141]
In the majority of the IR-based studies, IRs were rarely, if ever, documented in patient charts.[130-132]
OB was the most likely method to identify DRPs detected by other methods; all DRPs identified by IR or CH were detected by OB as well.[136]

Accuracy

Sensitivity, specificity, and predictive values of the different DRP assessment methods varied widely.
IR was generally more specific in identifying DRPS than the other methods.[124;129;142]
The rate of false positive DRPs has been reported to be 0% for IR, 0.3% for CH and 3.5% for OB.[124] In contrast, IR is consistently less sensitive when compared to TR.[124;129;143;144] The one study in which IR was found to be more sensitive than TR, interestingly, only included patient-reported IRs.[143]
The PPV ranged from 0 to 100% for trigger tool, depending upon the design of the rules or triggers.[127;137;139;142-144]

Resource utilization

While several studies provided information regarding resource utilization, only 7 studies provided numerical data.[124;127;133;138;140;144;145] These studies are displayed in Table 18.

Three studies provided comparative data regarding labor resource needs.[124;127;138] OB and CH were found to be more labor-intensive compared with either IR or TR.[127;138] TR was found to be the most time-efficient method.[127;144] However, this advantage for TR was observed only if the triggers had been previously validated and defined. Comparing TR to IR and OB, TR was documented to be the least labor-intensive method, followed by IR and OB, respectively.[124] Despite study limitations, including limited description of the cost of planning, training and evaluation, an automated IR was the least expensive methodology.[124;127;132-134;138;139]

While startup-costs were substantial, once fully established, TR was less expensive to perform when compared with CH.[140;145] One study documented that CH was associated with a cost of $68.70/ADR as compared to $42.40/ADR using TR.[140] When evaluating cost per drug dose, CH cost only $0.63 per dose compared to $4.82 for OB.[124]

Only one study, comparing IR and TR, evaluated both the cost and potential savings associated with DRP detection, and documented annual cost savings of $56,000 due to the avoidance of detectable DRPs.[144]

Additional findings

Depending upon the severity of the DRPs, certain methods may be superior to others. In general, IR detected more severe events, while CH was more likely to reveal moderate DRPs.[130]

The likelihood of reporting DRPs differed accordingly to health care practitioner, but no definite trend could be identified.[124;131;132;134;143]

DISCUSSION

To our knowledge, this study is the first investigation which has systematically compared commonly used DRP detection methodologies. Our findings suggest wide variation in the ability of the different methods to identify DRPs; in addition, some methodologies are superior to others depending upon the severity of the DRP. Lastly, substantial differences exist with respect to the accuracy and required labor to implement and utilize.

The publications reviewed in this paper varied considerably in terms of their purpose, setting, methods and definition of DRP. A wide variety of terms and definitions is used to describe medication safety.[146] While the World Health Organization makes specific recommendations regarding the definition of terms like ADE and ADR[147;148], no universally accepted definition for either term exists.[146;149;150]

The studies included in this review used a wide range of drug-related terms, including “adverse drug events”, “adverse drug reactions”, “medication errors”, “medication misadventures”, “medication administration errors”, as well as medication-related consequences, such as ”adverse events“, “unintended events”, and “intraoperative events”. Consequently, we used the term “drug-related problem” to encompass all definitions used in the studies.

Considerable inter-institution differences may exist depending upon the given methodology. As an example, IR systems can be either anonymous or non-anonymous reporting, which may impact upon the willingness of health care practitioners to report. Similarly, TR or IR can be manual or automated reporting; an automated system is likely to be more time-efficient, increasing the likelihood that health care practitioners will participate.

While we acknowledge that the above-stated variability can influence the comparability of the medication safety assessment studies, several definite trends are still indentifiable.

IR was the most frequently studied methodology, which is consistent with the fact that it’s known to be commonly used in health care systems for the detection and assessment of medication error and adverse drug events.[37] In addition, the collection of data through a voluntary IR system with a standardized form is considered relatively easy and generally at low cost. Of note, this method is recommended by the Institute of Medicine.[7;151]

While IR is recommended by many organizations, these systems are associated with substantial under-detection bias.[7;111;152-155] Our findings that IR was consistently inferior to other methods in reporting DRPs underscore this point. Reasons for underreporting include perceived lack of time and fear of consequences.[2;111;124;152] Only active institutionally encouraged reporting results in increased reporting of DRPs.[131;135;143] Patient-reported IRs, which potentially reveal DRPs not documented in the medical record, were rarely represented in the studies. However, these IRs may represent another viable approach in identifying DRPs.[143]

In comparison with IR, OB consistently identified the greatest number of DRPs. While it may capture the most DRPs, OB is more resource-intensive compared to IR and CH.[124] Considering its labor-intensiveness, OB must be performed over a relatively short period of time, which unfortunately results in only a brief snapshot of the medication use routine.[156] Consequently OB is not suitable for long-time tracking of DRPs.

In comparison with other systems, TR can examine the frequency and types of DRPs and also evaluate medication safety longitudinally over time.[105;111;142;153;157;158] According to three studies included in our review, once implemented, TR required the least resources.[127;140;144] A targeted process using specific triggers is more time-efficient, much less labor intensive than conventional CH and reproducible.[114;151;156;159-163] It is estimated that an assessment of 24 clearly defined triggers necessitates about 20 minutes of work time per chart.[111;157] The trigger tool is therefore suitable for a time-restricted approach.[154]

Although the IOM report on patient safety favors a computerized, validated set of triggers or alerts to detect DRPs[114], the use of a paper form without sophisticated computerized technology may make TR financially more feasible.[111;153] The IHI similarly champions the TR methodology.[157] Lastly, the Agency for Healthcare Research and Quality's "Critical Analysis of Patient Safety Practices" ranked computerized DRP detection with TR as "high strength of evidence" for its impact and effectiveness.[37]

The usefulness of a TR is particularly dependent upon its sensitivity and specificity. If validated appropriately, TR is as sensitive as CH and more sensitive than IR in identifying DRPs. The specificity of the method can be further enhanced if more stringent rules are applied.[128;155]

The achievement of a high positive predictive value (PPV) is obviously an important outcome and reduces the necessity of labor-intensive follow-up.[154;158;162;164;165] Depending on the validity of the triggers, PPV can range from 0 to 100%. The higher the PPV, the better the balance between review effort and DRP detection and follow-up.[166]

As demonstrated in this review, each method substantially differs in its detection of DRPs, and overlap between different methods is minimal. To reinforce this point, the reported agreement between IR and TR ranged from only 0.5 - 10%.[127;141]

While TR does not yield the greatest quantity of DRPs, it represents a time-efficient, practice-oriented method to assess medication safety.[123;130;142;143]

DRPs reported through IR may be more clinically significant than that reported via TR, which is reflected in the high PPV and low false positives associated with IR.[124] Its superior ability to detect events of high severity with a reliable specificity is particularly valuable toward the identification of sentinel events.[37;151;162] Non-punitive, confidential, simple and timely voluntary incident reporting can provide valuable background information for subsequent in-depth evaluations such as root cause analysis or trigger tool methodology.[2;105;157]

The relative strengths of IR and TR suggest that some combination of these two methodologies be used to optimally detect DRPs.[37;114;128;136;151;152;158;159;167]

It is important to note that retrospective DRP reporting is associated with relatively lower rates when compared with a prospective system.[13] However, both IR and TR allow a real-time identification of DRPs, which may reveal errors before they reach the patient, for example during the prescribing and administration stage.[168] Only one study included in this report assessed the methods specific to one or more component of medication use: in this study, OB identified 49.5% incorrect administration techniques, and CH detected 57.2% wrong dose errors, respectively.[138]

The introduction of new computer-assisted technologies in the medication use process may help to solve some of these problems. Poon at al. found that barcoding significantly reduced order transcription and drug administration errors.[59]

Other technologies such as computerized physician order entry and automated allergy and interaction checks may also decrease DRPs.[60;169;170] While new technologies can improve medication safety, they do not totally eliminate medication errors, and they can be associated with unintended consequences for error.[171] As an example, introduction of computer-generated alerts may result in order entry "fatigue" allowing for administration of potentially toxic drugs and doses. Therefore, institutionalized, proactive medication safety assessment remains an important tool in quality improvement processes. In addition, the significant amount of structured and therefore easy accessible data gained by using IT tools can provide new means for the medication safety assessment.

The studies included in this review varied widely in their purpose, setting, methods and nomenclature. In general, high quality comparative medication safety assessment studies are lacking, and standardization in medication safety assessment and language is insufficient.
The most commonly used methodologies differ in their accuracy, scope of identified DRPs, and cost associated with implementation. Therefore, accuracy, effectiveness and cost should be considered to meet institution-specific requirements.

Table 17: Overview of medication safety assessment studies with the primary aim of gathering comparative data

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Flynn[124] 2002 USA	Randomized study	Hospitals & skilled nursing facilities	1. Incident report review 2. Chart review 3. Direct observation	1. IR 2. CH 3. OB	Validity & cost-effectiveness in detecting MEs	ME: A medication error was defined as any discrepancy between the prescriber's interpretable medication order and what was administered to a patient.	ME rate: 17.9% IR: 0.2% CH: 3.7% OB: 67% CH=IR: 4%	False positives: IR: 0% CH: 0.3% OB: 3.5% Interrater agreement: 91.4% κ CH: 0.87 κ OB: 0.74	By provider: Pharmacy technicians were more efficient and accurate than R.N.s and L.P.N.s in collecting data about MEs
Katz[125] 2000 USA	Prospective study	1 hospital, anesthesiology patients	1. Traditional incident reporting of non-physician-personnel 2. Anesthesiologist self-reporting 3. Medical chart review	1. IR 2. physIR 3. CH	To compare reporting sources for perioperative outcomes and identify factors that might improve data capture	AOs: Adverse outcomes were considered to be all instances of patient harm that could potentially be related to anesthesia, whether transient or permanent.	AO rate: 1-9% of anesthesias AO identification: IR: 9.1% physIR: 71% CH: 38% IR=physIR: 0.8% IR=CH: 0.8% physIR=CH: 16.2% IR=physIR=CH: 0.8%	No numeric data provided	By type: No statistically significant difference in rates of self-reporting by anesthesiologists according to pre-existing disease, severity of outcome or human error. IR identified more human errors. More reports for disabling AOs.
Haw[126] 2007 UK	Cross-sectional, observational study	1 psychiatric hospital, geriatric long-stay patients	1. Directly observed medication administration errors 2. Incident reporting 3. Retrospective chart review	1. OB 2. IR 3. CH	To investigate the frequency, type and severity of directly observed medication administration errors compared with errors detected by retrospective chart review and incident reports.	ME: A deviation from a prescriber's valid prescription or the hospital's policy in relation to drug administration, including failure to correctly record the administration of a medication.	ME rate: 25.9% ME detection: OB: 369 MEs IR: 0 MEs CH: 148 MEs CH=OB: 100%	No data provided	By process: The commonest error types, were crushing tablets without the authorization of the prescriber (28.7%), omission without a valid clinical reason (27.1%), failing to sign the medication chart to record that a drug had been administered (23.6%) and wrong quantity (8.7%). Proportionally fewer errors were made at the 22.00 h medication round than at other rounds
Jha[127] 1998 USA	Prospective, cohort study	1 tertiary care hospital	1. Stimulated voluntary report 2. Chart review 3. Computer-based monitoring	1. eIR 2. CH 3. TR	To develop a computer-based ADE monitor, and to compare the rate and type of ADEs found with the monitor with those discovered by chart review and by stimulated voluntary report.	ADE: Definition of 52 rules	ADE rate: 2/100 admissions ADE identification: eIR: 4% CH: 65% TR: 45% eIR=TR: 0.5% CH=TR: 12% Potential ADEs: eIR>CH, TR	PPV: TR: 16%-23% Interrater agreement: TR κ: 0.53 (89%) CH κ: 0.81 κ preventability: 0.92 κ severity: 0.37	By severity: High severity: TR>CH (51% vs. 42%, p = .04) By type: Symptom changes: CH>TR, eIR Lab changes: TR>CH, eIR Preventability: CH>TR

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Neubert[128] 2006 Germany	Prospective survey	1 university hospital, pediatric patients	1. Reporting by the treating physician 2. Intensive chart review 3. Automatic laboratory signals	1. physIR 2. CH 3. TR	To evaluate a computerized monitoring system based on laboratory test results for the detection of ADRs on a pediatric ward.	ADR: WHO-definition	ADR rate: 13.1% of patients ADR detection: ADRs: 73 physIR: 42.5% CH: 100% (CH only: 19) TR: 42.4% (TR only: 23) CH=TR: 8	Sensitivity: TR: 90.3% Specificity: TR 19.6%	By severity: TR detects mainly mild ADRs By type: Systems detect different ADRs.
Berry[129] 1988 USA	Observational study	1 teaching hospital	1. Voluntary reporting 2. Pharmacist screening of medication orders 3. Screening of laboratory reports	1. IR 2. pharmCH 3. TR	To determine the sensitivity and specificity of 3 methods detection ADRs.	ADR: (WHO) Any noxious or unintended response to a drug that occurs at doses usually for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.	ADR rate: 13.3% of patients ADR identification: total: 13 IR: 0 pharmCH: 13 TR: 11	Sensitivity: IR: 0% pharmCH: 54.5% TR: 100% Specificity: IR: 100% pharmCH: 81.6% TR: 56.3%	No data provided
Hogan[130] 2008 England	Retrospective study	1 acute care hospital, medical / surgical patients	1. The clinical incident database 2. Case note review 3. (Health and safety incident database) 4. (Complaints database) 5. (Claims database) 6. (Inquest database) 7. (Patient administration database)	1. IR 2. CH	To assess the utility of 7 data sources already existing within hospitals for monitoring patient safety.	AE: An unintended injury or complication of care leading to prolonged admission, disability at discharge or death and caused by healthcare management rather than the disease process.	PSI rate: 32.3% AE rate: 18.1% PSI identification: total incidents: 10'190 IR: 484 CH: 8781 (estimated) CH=IR: 3	PPV: CH: 56.3%	By severity: Death/severe: CH<IR Moderate: CH>IR By type: IR: 37.5% MEs and equipment failures
Kunac[131] 2008 New Zealand	Prospective, observational, cohort study	1 university hospital, pediatric patients	1. Concurrent routine hospital-incident reporting system 2. Solicited reports from staff 3. Chart review for all admissions 4. (Interview of parents)	1. IR 2. eIR 3. CH	To evaluate the frequency and characteristics of preventable medication-related events in hospital-ised children, to determine the yield of several methods for identifying them and to recommend priorities for prevention.	Medication related events: Encompassing ADEs, preventable ADEs, ADRs, potential ADEs, harmless medication errors, trivial rule violations, others.	Medication-related event detection: IR: 0.53% eIR: 14.6% CH: 83.3% duplicates: 14 of 761 reports	No data provided	By type: preventable events: ADEs: 56.7% By process: most common ADEs: (CI 95%) improper dose, prescribing By provider: nurses: 59% > pharmacists

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Tam[132] 2008 Hong Kong	Comparative study	4 primary care clinics	1. Voluntary reporting 2. Patient survey for identifying medication misadventures 3. Chart review	1. IR 2. pIR 3. CH	To compare the strengths and weaknesses of voluntary reporting, chart review and patient survey in measuring medication misadventures in general practice.	Medication misadventure: Sum of medication error, adverse drug reaction and adverse drug event.	Medication misadventure rate: 0.64% of medication orders (CI 95%, 0.58 - 0.70%) IR: 0.52% of drug orders MEs: 0.34% ADEs: 0.18% pIR: 1.46% of drug orders MEs: 0.42% ADEs: 1.04% CH: 2.03% of drug orders MEs: 4, 0.07% ADEs: 107, 1.96% Overlap: minimal	No data provided	By severity: IR least powerful for potential & preventable ADEs By provider: Doctors (62.2%) Pharmacists (6.7%) Nurses (6.3%)
Olsen[133] 2007 England	Prospective, cohort study	1 district hospital, medical/surgical patients	1. Incident reports, 2. Record review at time of discharge 3. Active surveillance of prescription charts by pharmacists	1. IR 2. CH 3. pharmCH	To assess three practical methods of detecting adverse events and potential adverse events in order to consider their respective contributions to information on safety and quality in a designated hospital.	AE: An unintended injury or complication, caused by healthcare management rather than the disease process, which prolonged the admission or led to disability at discharge or death.	AE rate: 4% of patients IR: AEs: 0 CH: AEs: 26 pharmCH: AEs: 10	Correlation between assessors: poor (k,0.2)	By process: Most common AEs: Failure to prescribe regular or indicated medication (15/30) and failure to prescribe the correct dose of a drug (9/30).
Bennett[134] 1977 USA	Observational study	1 teaching hospital, medical / surgical patients	1. Hospital-wide voluntary reporting system 2. Short-term, intensive, prospective surveillance system	1. IR 2. CH	To examine the feasibility of establishing an ongoing ADR monitoring and reporting program in comparison with a voluntary reporting system.	ADR: Any response to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis, or therapy, excluding therapeutic failures, intentional and accidental poisonings, and drug abuse.	ADR rate: IR: 0.08% of patients CH: 7.2% of patients (CH surgical: 5.9%) (CH medical: 9%)	No data provided	By provider: Nurses (6) > Physicians (2) By type: Definite/probable: IR: 33% CH surgical: 26% CH medical: 29%

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Stanhope[36] 1999 UK	Retrospective review	1 hospital	1. Adverse incidents reported by staff to the maternity risk manager 2. Incidents detected by each risk manager, but not reported 3. Full retrospective case note review	1. IR 2. CH risk 3. CH full	To determine the reliability of AI reporting by establishing what proportion of AIs were not reported by staff and whether a risk manager can increase the reliability of AI reporting by searching through various types of documentation.	AEs: Rated by an incident list MEs: No data provided	AI identification: IR: 23% CH risk: 22.4% CH full: 54.6% ME identification: minor, moderate IR: 1 CH risk: 1 CH full: 44	Interrater agreement: No discrepancies reported	By severity: IR serious: 48% CH serious: 16% IR moderate: 25% CH moderate: 30% IR minor: 15.2% CH minor: 22% By profession: Midwives reported more AIs (13.3%) than physicians (9.7%)
Bates[135] 1993 USA	Prospective, cohort-study	1 urban tertiary care hospital	1. Incident reporting by nursing and pharmacists 2. Solicited incident reporting 3. Daily chart review	1. IR 2. eIR 3. CH	To evaluate the incidence and preventability of ADEs and to determine the yield of several strategies for identifying them.	ADE: An injury resulting from the administration of a drug.	ADE rate: 6/100 admissions 27/2967 patient days IR + eIR: 59% IR: 37% eIR: 22% CH: 41% ADE identification: CH only: 67% Not identifiable by chart: 1	Interrater agreement: Preventability: K 0.71-0.91	No data provided
Capuzzo[136] 2005 Italy	Prospective study	1 teaching hospital, ICU patients	1. Voluntary, facilitated and not necessarily anonymous UE reporting with a structured form 2. Observing of unaware staff	1. IR 2. OB	To compare the reporting of UEs between staff and observer in an intensive care unit.	UE: Any UE that reduced or could have reduced the safety margin for the patient while in ICU was considered. UEs occurring during transport or in other areas of the hospital were not considered.	UE identification: eIR: 26.9/100 patient days (CI 95% 16.9–37.0) OB: 53.1 per 100 patient days (CI 95% 40.6–65.6) all IRs=OR 21 undetected by IR	Agreement between staff and observers: 0.869 intraclass correlation coefficient	By type: Systems detect different ADRs. By process: The incidence of UE detection during morning shifts was significantly higher than during afternoon or night shifts ($p < 0.001$).
Egger[137] 2003 Germany	Prospective, observational study	1 geriatric rehab	1. Patients screened for ADRs by a pharmacoepidemiological team 2. ADRs predicted by a computerized drug database	1. OB 2. TR	To compare the rate of ADRs (DDIs) as predicted by a computerized pharmacological database to the actual rate determined by direct observation in a sample of geriatric patients.	ADR: (WHO) A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.	ADR rate: 60.7% of patients DDI rate: 44.7% ADR identification: OB: 153 (0.9/patient) TR: 64 (41.8% of patients) DDI: OB: 14.7% of patients TR: 12/patient	TR PPV: ADR 1.8% TR sensitivity: ADR 47.5% DDI 58.3% TR specificity: 1.6%	No data provided

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Takata[5] 2008 USA	Surveillance study	5 pediatric hospitals	1. Voluntary incident reports 2. Pharmacist identified MEs 3. order that contains a validated pediatric trigger method	1. IR 2. OB 3. TR	To determine baseline ME and ADE rates and characterize MEs and ADEs in pediatric patients in the prescribing and ordering process. Secondary objective: to affirm the effectiveness of a trigger tool using electronic records for ADE identification compared with that of voluntary incident reporting.	ADE: An injury, large or small, caused by the use (including non-use) of a drug. This may be as harmless as a drug rash or as serious as death from an overdose.	ADE identification: (CI 95%) IR: 1.7/1000 days OB: 2.67/1000 days TR: 22.3/1000 days	PPV: TR: 4.7% (95% CI, 3.7–5.8%) Interrater agreement: 85%	By type: probability of ADEs: TR>IR Most common error type: overdose (63%; 95% CI, 58–68%), underdose (14%; 95% CI, 10–18%), and wrong drug (8%; 95% CI, 5–11%).
Dormann[139] 2004 Germany	Prospective survey	1 university hospital	1. Daily chart review by physicians and clinical pharmacists 2. Computer-generated daily list of automatic laboratory signals and alerts of ADRs, including patient data and dates of events.	1. CH 2. TR	To investigate the effectiveness of a computer monitoring system to detect ADRs and to compare it to chart reviews.	ADR: (WHO) a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function	ADR identification: total: 109/377 patients CH<TR CH=TR: 61 CH only: 3 TR only: 39 not alerted by TR: 9	PPV: TR: 32% Sensitivity: TR: 91% Specificity: TR: 76%	By provider: 61.5% by physician Physician only: 6 reports
Hope[140] 2003 USA	Comparative study	2 study cites Indianapolis (I): 22 ambulatory clinics Boston (B): 11 ambulatory clinics	1. Traditional, pharmacist based review process 2. Electronic medical record review	1. CH 2. TR	To describe a process of ADE and ME identification and compare review of ADEs and MEs by the two methods of review.	ADE: Harm associated with a drug. ME: An error in the medication use process including the prescribing, transcribing, administering, and monitoring steps.	TR signals: I: 5824; B: 2492 total alerts: 11602 CH ADEs: I: 242; B: 535 CH MEs: I: 104; B: 562	ADE PPV TR: I:10.2% B: 9.6% (p – 0,36) ME PPV TR: I: 4.4% B: 10% (p < 0:001)	No data provided

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Sari[141] 2006 UK	Two stage, retrospective patient case not review	1 large NHS hospital	1. Review of patient safety incidents reported by routine reporting system 2. Case not review by nurses, using 18 explicit criteria	1. IR 2. TR	To evaluate the relative performance of a routine incident reporting system in identifying patient safety incidents comparing it with a well validated method.	PSI: Any unintended event caused by the health care that either did or could have led to patient harm. AEs Patient safety incidents causing harm to patients	PSI rate: 22.9% of admissions (CI 95%; 20.3% to 25.5%) ADR identification: PSI identification: IR: 7% TR: 83% IR=TR: 10% AE rate: 10.9% (CI 95%, 9.0% to 12.8%) AE identification: IR: 5% TR: 100%	Interrater agreement: TR: 84-90% (CI 95%) TR: κ 0.67-0.76	By severity: TR>IR
Ferranti[142] 2008 USA	Retrospective review	Tertiary care pediatric hospital	1. Voluntary safety reporting 2. Computerize ADE detection system	1. IR 2. TR	To identify the most deleterious drug classes to pediatric inpatients and determine which detection methodology provides the greatest opportunity to reduce harm.	ADE: An injury resulting from the use of a drug, involving errors of omission where the initial drug order never reached the patient and harm resulted.	ADE rate: 1.6/1000 patient days 1.8/100 admissions IR: 93 (849 reports) ADE identification: TR: 78 (1573 alerts) IR=TR: N=4 (IR>TR)* *rates not statistically significant	PPV: IR: 11% TR: 5.1% Interrater agreement: κ IR : ≥ 0.88	By type: IR identified more systems failures (e.g., drug administration errors) while TR detected events caused by high-risk medications. Omission: IR only
Weissman[143] 2008 USA	Randomized sample survey	Adults previously hospitalized for medical or surgical treatment at Massachusetts hospitals	1. Post-discharge patient interview 2. Computerized medical record review	1. pIR 2. TR	To compare AEs reported in post-discharge patient interviews with AEs detected by computerized medical record review	AE: Unintended harm to the patient by an act of commission or omission rather than by the underlying disease or condition of the patient.	AE identification: total: 304 pIR: 253 TR: 182	PPV: pIR: 23.1% TR: 50.5% Sensitivity: pIR: 50.5% TR: 23.1% Specificity: pIR: 80.3% TR: 93.2% Interrater agreement: [95% CI] κ IR: 0.85-0.97 κ CH: 0.61-0.96 κ IR/CH: 0.20 IR=CH: 79%	By provider: Patients report many events that are not documented in the medical record.

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Dormann[144] 2000 Germany	Prospective, controlled cohort study	1 university hospital, medical patients	1. Stimulated spontaneous reporting 2. Automatically generated laboratory signals and reports	1. eIR 2. TR	To implement a computer-based adverse drug reaction monitoring system and compare its results with those of stimulated spontaneous reporting.	ADR: WHO definition	ADR rate: 12% of patients ADR identification: eIR: 4.5% TR: 9% eIR=TR: 5 of 46 ADRs	PPV: TR: 13% Sensitivity: eIR: 37% TR: 74% Specificity: eIR: 98% TR: 75%	By severity: Serious ADRs: 3 TR: 3 eIR: 2 By type: Predictable ADRs: 48%; detected by TR only By provider: ADRs not recognized by a physician : 63%
O'Neil[145] 1993 USA	Cohort study	1 academic teaching hospital, medical patients	1. Concurrent physician reporting mechanism using the hospital electronic mail system 2. Retrospective record review using a screening mechanism	1. physIR 2. TR	To assess the effectiveness of house staff physician reporting as a method for identifying adverse events on a medical service and to compare the physician reporting mechanism with a retrospective record review mechanism.	AE: An injury that prolongs the hospital stay or leads to disability at the time of discharge, which is caused by inappropriate medical management instead of the disease process.	AE identification: physIR: 66.9% TR: 63.9% physIR=TR: 41/133	False positives: physIR: 35/124 TR:1854/3128 Interrater agreement: κ physIR=TR: 0.52	By type: Preventable ADEs: physIR>TR The house staff did report statistically more preventable AEs (62.5% compared with 32%; *P*-0.003)
Kilbridge[172] 2006 USA	Prospective cohort-study	1 university hospital, 1 community hospital	1. Voluntary reporting 2. Automated surveillance	1. IR 2. TR	To compare the rates and nature of ADEs at an academic medical center and a community hospital using a single computerized ADE surveillance system. Findings were compared with voluntary reporting.	ADE: List of 69 rules.	ADE rate university: 4.4/100 admissions ADE rate community: 6.2/100 admissions ADE identification: university hospital: IR: 144 TR: 520 community hospital: IR: 23 TR: 283	Interrater reliability: κ >0.88 for causality and severity	No data provided

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Shannon[138] 1987 USA	Retrospective study	30 long term care nursing facilities	1. Observation of medication administered for 20 residents 2. Traditional retrospective review of 10% of residents' charts	1. OB 2. CH	To compare two methods of detecting MEs in long term care facilities.	MEs: MEs are doses not administered in accordance with the written orders of the attending physician, encompassing drug omission, unauthorized drug, wrong dose, wrong route, and wrong dosage form, incorrect administration technique and omission of documentation.	ME rates: OB: 9.6% CH: 0.2%	Interrater variability: not significant (Kruskal-Wallis test, H=4.98, p>0.30)	By process: OB: 49.5% incorrect administration technique CH: 57.2% wrong dose
Powell[173] 2007 USA	**AEs** observational	1 hospital, anesthesia patients	1. Voluntary disclosure of AEs 2. Queries of anesthesia information management systems 3. (database queries followed by human clarification)	1. IR 2. TR	To analyze the automated queries reporting in order to evaluate the role of man and machine in anesthesia AE reporting.	AE: No data provided	AE identification: IR only: 28.9% TR only: 28.9%	No data provided	No data provided
Schade[174] 2006 USA	Prospective cohort-study	1 rural acute hospital	1. Occurrence reporting tool 2. Targeted chart audits for antidotes	1. IR 2. TR	To determine: If ADEs are as underreported as the literature suggests. The feasibility of tracking the accuracy of hospital ADE self-reporting by comparing ADEs recorded in an occurrence reporting tool with those detected by surveillance of rescue drugs.	ADE: An adverse event that occurs following the administration of a drug *in the hospital*, whether or not the patient was an inpatient at the time, excluding events following drugs administered outside of the hospital and including events following drugs given in the hospital's outpatient or emergency department.	ADE rate: 3% of discharges ADE identification: IR: 4 TR: 109	Specificity: Rescue drugs have only low specificity	By severity: IR: higher proportion of moderate to severe ADEs By type: preventable ADEs: 0.8% of discharges Mainly dose-related toxicity (47%), followed by allergic reactions (36%).

Reference	Study design	Setting	Methods compared	Method categorization	Outcome measures	Definition	Results		
							DRP rates	Validity	Additional findings
Classen[175] 2005 USA	Prospective study	1 university hospital	1. Voluntary spontaneous reporting 2. Computerized voluntary ADE reporting 3. Computerized ADE monitor	1. IR 2. IR using TR 3. TR	To develop a new method to improve the detection and characterization of ADEs in hospital patients.	ADE: (WHO) An ADE is one that is ''noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions.'' This definition excluded therapeutic failures, poisonings, and intentional overdoses.	ADE rate: 1.67% of patients ADE identification: ADEs: 731 IR: 9 IR via TR: 92 TR: 631	No data provided	No data provided

Abbreviations:

ADE	adverse drug event	DRP	drug-related problem	ME	medication error
ADR	adverse drug reaction	IHI	Institute for Healthcare Improvement	OB	observation
AE	adverse event	IR	incident reporting	PPV	positive predictive value
AI	adverse incident	eIR	encouraged / solicited incident reporting	PSI	patient safety incident
AO	adverse outcome	pIR	patient incident reporting	R.N.	registered nurse
CH	chart review	physIR	physician incident reporting	TR	trigger tool
pharmCH	review of prescription charts by a pharmacist	K	Kappa value	UE	unintended event
DDI	drug-drug-interaction	L.P.N	licensed practical nurse	WHO	World Health Organization

Table 18: Studies providing numeric data on effort and cost of the evaluated medication safety assessment methods

Reference	Study design	Practice setting *specialty*	Observation period *Study size*	Type of DRP investigated	Methods compared	Resource utilization	
						Effort	**Cost**
Flynn[124] 2002 USA	Randomized study	36 hospitals & skilled nursing facilities *No data provided*	No data provided *No data provided*	MEs	IR vs. CH vs. OB	IR: 10.3-18.57 min. CH: 1.21-2.61 min. OB: 13. –15.97 min.	CH: $ 0.63/dose OB: $ 4.82/dose
Jha[127] 1998 USA	Prospective, cohort-study	1 tertiary care hospital *No data provided*	9 months *Patient days: 21964*	ADEs	IR vs. CH vs. TR	TR: 11 hrs/week CH: 55 hrs/week TR<CH 1 full-time equivalent needed	No data provided
Olsen[133] 2007 England	Prospective, cohort-study	1 district hospital *Medical / surgical*	No data provided *Patients: 288*	AEs	IR vs. CH	0.5-0.9% of total annual working hours	No data provided
Hope[140] 2003 USA	Comparative study	2 study sites Indianapolis (I): *22 ambulatory clinics* Boston (B): *11 ambulatory clinics*	4 months *No data provided*	ADEs & MEs	CH vs. TR	No data provided	Cost/ADE incl. follow-up CH: $ 68.70 TR: $ 42.40
Dormann[144] 2000 Germany	Prospective, controlled cohort-study	1 university hospital *Medical*	6 months *Patients: 379* *Treatment days: 1718*	ADRs	IR vs. TR	Time: CH>TR	Potential savings / ward and year $ 59'600/year [1999 values]
O'Neil[145] 1993 USA	Cohort-study	1 academic teaching hospital *Medical*	34 months *Admissions: 3141*	ADEs	IR vs. TR	IR: data not provided CH: 532 hours	IR: $ 15,323 TR: $ 54,462
Shannon[138] 1987 USA	Retrospective study	30 long term care nursing facilities *No data provided*	No data provided *No data provided*	MEs	OB vs. CH	Mean time per chart or patient: OB: 9.18 min. CH: 11.56 min.	No data provided

Abbreviations:

ADE	adverse drug event	DRP	drug-related problem	ME	medication error
ADR	adverse drug reaction	IHI	Institute for Healthcare Improvement	OB	observation
AE	adverse event	IR	incident reporting	PPV	positive predictive value
AI	adverse incident	eIR	encouraged / solicited incident reporting	PSI	patient safety incident
AO	adverse outcome	pIR	patient incident reporting	R.N.	registered nurse
CH	chart review	physIR	physician incident reporting	TR	trigger tool
pharmCH	review of prescription charts by a pharmacist	K	Kappa value	UE	unintended event
DDI	drug-drug-interaction	L.P.N	licensed practical nurse	WHO	World Health Organization

CONCLUSION

All four assessment techniques have different strengths and weaknesses. In addition, overlap between different methods in identifying DRPs is minimal. While TR appears to be the most effective and labor-efficient method, IR best identifies high severity DRPs. Consequently, the review of the use of combination methodologies, such as the TR with IR, is strongly recommended for the future. Prospective, controlled trials comparing these methodologies are needed to clarify the optimal management of DRPs.

In the light of these findings, the following chapters are dedicated to the discussion of a practice-oriented approach to the techniques of trigger tool and incident report review.

CHAPTER 4

Medication use evaluation via manual trigger tool methodology in the inpatient setting

ABSTRACT

Background

Regulatory agencies require health care institutions to regularly assess the safety of medication use through active monitoring.

Intravenous (IV) heparin for anticoagulation therapy is one of the drugs considered high-risk by The Institute for Safe Medication Practices. The indicator or trigger tool technology is considered an efficient and effective tool for medication safety assessment.

The aim of this study was to develop and pilot a manual trigger tool for the assessment of processes involving IV heparin use.

Method

A systematic literature review (Pubmed, Embase, Scopus) was undertaken in order to identify recommended medication safety indicators. Indicators addressing the defined process outcomes of IV heparin therapy (adequate prescribing, dispensing, administration, monitoring, and dose adjustments) were integrated into a manual trigger tool form and critically assessed by the thrombosis and hemostasis committee. Subsequently, the manual trigger tool was piloted with 20 randomly selected inpatients and repeated one year later.

Results

The literature search identified 79 indicators. Nineteen were used for the manual trigger tool form. The triggers successfully addressed the following therapeutic quality endpoints: use of the order form, therapy initiation, monitoring, time to therapeutic goal, and adequacy of dose adjustments. Completion of the trigger tool form necessitated 20 minutes per patient.

Discussion

The inclusion of only 20 randomly selected patients in a once-yearly assessment allowed the identification of critical aspects of IV heparin therapy involving different steps of the medication use process. However, the trigger tool was less valuable for the detection of problems with transcribing / documenting, dispensing by pharmacy and patient education.

Conclusion

A manual trigger tool form, developed based on expert consensus, was an efficient tool for the assessment of IV heparin use and the supervision of improvement projects. For a comprehensive monitoring of medication safety, indicators should address all aspects of the medication use process.

BACKGROUND

Drug related problems (DRPs) represent a major threat to patient safety in health care institutions.[176] DRPs cause approximately 5-7% of all hospital admissions and 7.5 – 20% of all inpatients experience DRPs, signficantly prolonging hospital stay.[13;177-179] Importantly, 47% to 76% of all DRPs are preventable.[180-183]

Only limited data on DRPs in Swiss institutions is available:

Among 6383 medical inpatients analyzed in two Swiss primary care teaching hospitals, 481 (7.5%) experienced at least one DRP during their hospital stay; 0.4% (95% CI; 0.2 - 0.7%) of the events were associated with a medication error.[14;50] Approximately 4% of the patients were admitted to the hospital because of a DRP.[50]

In 1999, Lepori et al. estimated that the cost associated with drug-related hospital admissions due to inappropriate or unnecessary drug treatment was 12'000–16'000, with direct annual extra costs of 70–100 million Swiss francs.[15] This finding has been confirmed in the international literature as well.[51]

Regulatory agencies require health care institutions to regularly assess the safety of medication use through active monitoring, identifying the most common DRPs and developing the necessary strategies to manage high-risk drugs.[108;118] Procedures associated with their use should be assessed routinely and the results should be incorporated into prevention strategies.

Unfractionated heparin (UFH), a drug commonly used in prophylaxis and treatment of thrombotic disorders[184], is one of the agents highlighted as a high-risk drug by the Institute for Safe Medication Practices (ISMP).[110]

UFH is approved by the Food and Drug Administration (FDA) for use in thrombotic disorders. In addition, UFH has demonstrated efficacy in acute coronary syndrome, STEMI, and unstable angina.[184] An overview of approved indications and common off-label use is detailed in Table 19:

Table 19: UFH indications [184]

FDA approved indications	Unapproved indications
1. Anticoagulation 2. Atrial fibrillation 3. Pulmonary embolism 4. Venous thromboembolism prophylaxis & treatment	1. ACS 2. STEMI 3. unstable angina

In order to improve medication safety through targeted, institution-individual projects, hospitals need to measure meaningful baseline and post-improvement data.

In order to quantify DRPs efficiently, different methods have been discussed in the actual literature. While chart review might provide the best insight into individual cases, this methodology is very expensive in terms of cost and personnel required. The indicator technology (also referred to as trigger tool) is considered more efficient yet highly effective.[34]

The aim of this indicator project was to develop and pilot a reliable indicator-based spreadsheet (trigger tool form) for the targeted, efficient manual collection of baseline data on the quality of heparin therapy processes in the inpatient environment and for the supervision of projects intended to improve medication safety processes evolving around heparin use.

METHOD

Development of the trigger tool spreadsheet

A systematic literature review, using Pubmed, Embase and Scopus databases was undertaken in order to identify recommended medication safety indicators.

The following search strategy was applied:

Indicator [TITLE] AND drug safety [ANY]:	223
Indicator [TITLE] AND medication safety [ANY]:	3
Trigger [TITLE] AND drug safety [ANY]:	10
Trigger [TITLE] AND medication safety [ANY]:	75

No time or language restrictions were applied. References in the retrieved articles were also reviewed for additional relevant articles. After screening of the abstracts, all relevant full-text articles were retrieved.

The process-related indicators for the evaluation of the drug therapy quality were derived from the literature, consensus-based among clinical pharmacists; one of the clinical pharmacists a specialist in anticoagulation therapy management, and three of them specialists in the field of medication outcomes research. In addition to the indicators suggested in the literature, additional indicators suggested by the experts were also considered for inclusion.

Indicators derived from the literature review and suited to address the defined outcomes were integrated into a spreadsheet, called manual UFH trigger tool. In addition, a data collection sheet was developed for the analysis of the pilot phase and follow-up study 12 months later.

Subsequently, the spreadsheet was referred to the interdisciplinary thrombosis & hemostasis committee for approval.

Piloting of the UFH trigger tool

Twenty patients treated with UFH were randomly selected for inclusion into the pilot. The pharmacy system WORX allowed for automated screening for patients treated with UFH. The preliminary selection of patients was performed according to the following selection criteria:

Inclusion criteria

- The patient was treated with UFH during a specific time period, chosen for the pilot.
- The patient was treated with UFH during at least 3 days.
- The patient was already discharged or past the 3 initial days of the initiation of the UFH therapy.

Exclusion criteria

- Pregnant at the time of the pilot or an obstetrics / gynecology inpatient (reason for exclusion: utilization of different guidelines).
- Pediatric inpatient, e.g., younger than 18 years (different guidelines).
- UFH was already initiated at an outside hospital prior to the patients' admission.
- Intensive care unit when heparin therapy was started (different opportunities and rules for supervision and therapy management).

Overall, 2 patients had to be excluded due to not complying with the initial inclusion criteria and were replaced.

The necessary patient-information was manually obtained through the electronic hospital pharmacy information system, the electronic inpatient record, the automated nursing medication administration record, and the laboratory database. The data were collected retrospectively and for a maximum of 3 days of observation from heparin initiation.

The results were independently analyzed by two pharmacists, compiled in a comprehensive report and handed over to the thrombosis & hemostasis committee, the medication safety committee as well as to the pharmacy & therapeutics committee.

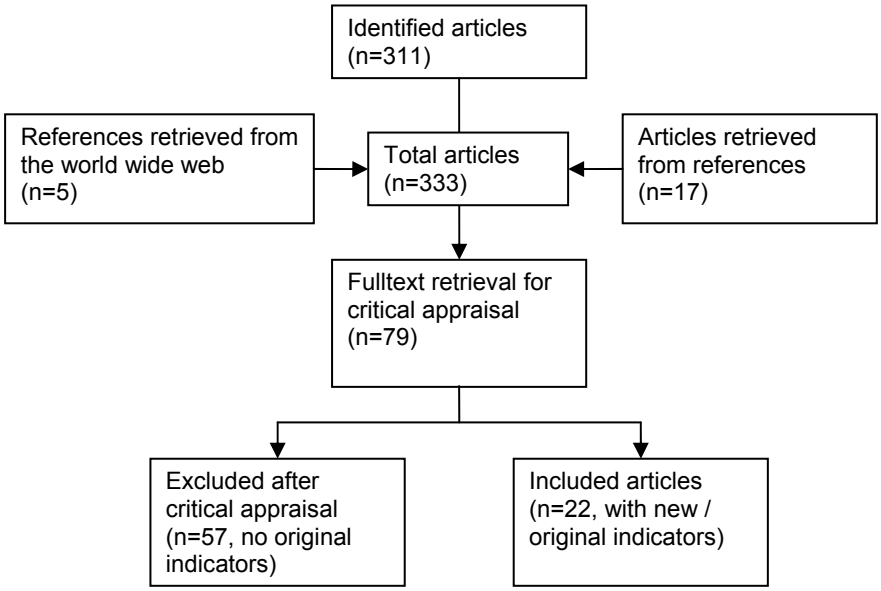
After 12 months and an adjustment of the UFH order set, the medication use evaluation was repeated.

RESULTS

Development of the trigger tool spreadsheet

Based on a thorough literature review, a total of 333 indicators were identified addressing medication safety issues. Seventy-nine of these 333 medication safety indicators involved anticoagulation. Details on the literature research are displayed in figure 2.

Figure 2: Overview of inclusion and exclusion of articles



Based on a consensus with the experts of the thrombosis & hemostasis committee, the following indicators were introduced into the manual UFH trigger tool:

- Collection of basic patient data (age, weight, allergy information)[8]
- Correct prescription: use of the appropriate form (correct indication, correct form)[185;185]
- Correct prescription: calculation of the initial dose (weight-based)[185;185]
- Existence of baseline labs[150;186]
- Application of the appropriate product[187]
- Appropriate administration technique[188;189]
- Adequate calculation of the pump administration rate (application of the prescribed dose)[188;189]
- Timeliness of follow-up labs[150;190-192]
- Presence of low platelet count[150;190;191]
- Presence of thrombocytopenia[150;190;191]
- Presence of elevated aPTT[150;186;190;191;193;194]
- Presence of a sub-therapeutic aPTT[150;186;190;191;193;194]
- Presence of HIT[166;195]

- Timeliness of drug administration[new]
- Timeliness of adjustment to lab values[new]
- Inappropriate use of intramuscular drugs[162;196]
- Application of the antidote protamine[35;194]
- Transfer to a higher level of care due to DRPs[35;194]
- Pharmacy intervention necessary[new]

The following endpoints were considered the most important indicators for appropriate UFH therapy and management processes by the experts involved in the indicator development project:

- Appropriate bolus dosing based on patient weight
- Appropriate timing of lab follow-up (aPTT, INR, PT levels)
- Frequency of appropriate dose adjustment based on the institution's protocol
- Correct initial continuous infusion calculations

The manual UFH trigger tool spreadsheet is displayed in figure 3.

Piloting of the UFH trigger tool

A table, focusing on process-related indicators, was developed in order to display the results collected in the trigger tool spreadsheet in a clearly laid out manner (Table 20).

Table 20: UFH trigger tool data collection sheet

DEMOGRAPHICS				INITIATION				MONITORING				THERAPY STOP / INTERRUPTION
Name	MRN	Unit	Indication	Heparin form used	Bolus dose (Y/N)	Correct bolus dose calculation (Y/N)	Correct infusion rate calculation (Y/N)	Number of aPTT levels drawn	Number of appropriate timing of lab draws	Number of proper dose adjustments in response to aPTT	Number of aPTT labs that should have been drawn	Reason for therapy stop / interruption of heparin

The use of the trigger tool annually for 2 years allowed for the detection of the following:

- The use of the order form vs. no use of the order form
- The use of the correct order form (if different order sets for different indications are available)
- The appropriate initiation of the UFH therapy (weight-based or aPTT-based bolus calculation and calculation of the infusion rate)
- The appropriate monitoring of the UFH therapy (time of labs drawn, interval of labs drawn, amount of labs drawn
- The time to therapeutic range
- The time to and appropriateness of dose adjustment.

The details of two trigger tool analysis addressing process-relevant aspects of UFH therapy performed in 2008 and 2009 are displayed in Table 21.

Table 21: Comparative findings from 2008 and 2009

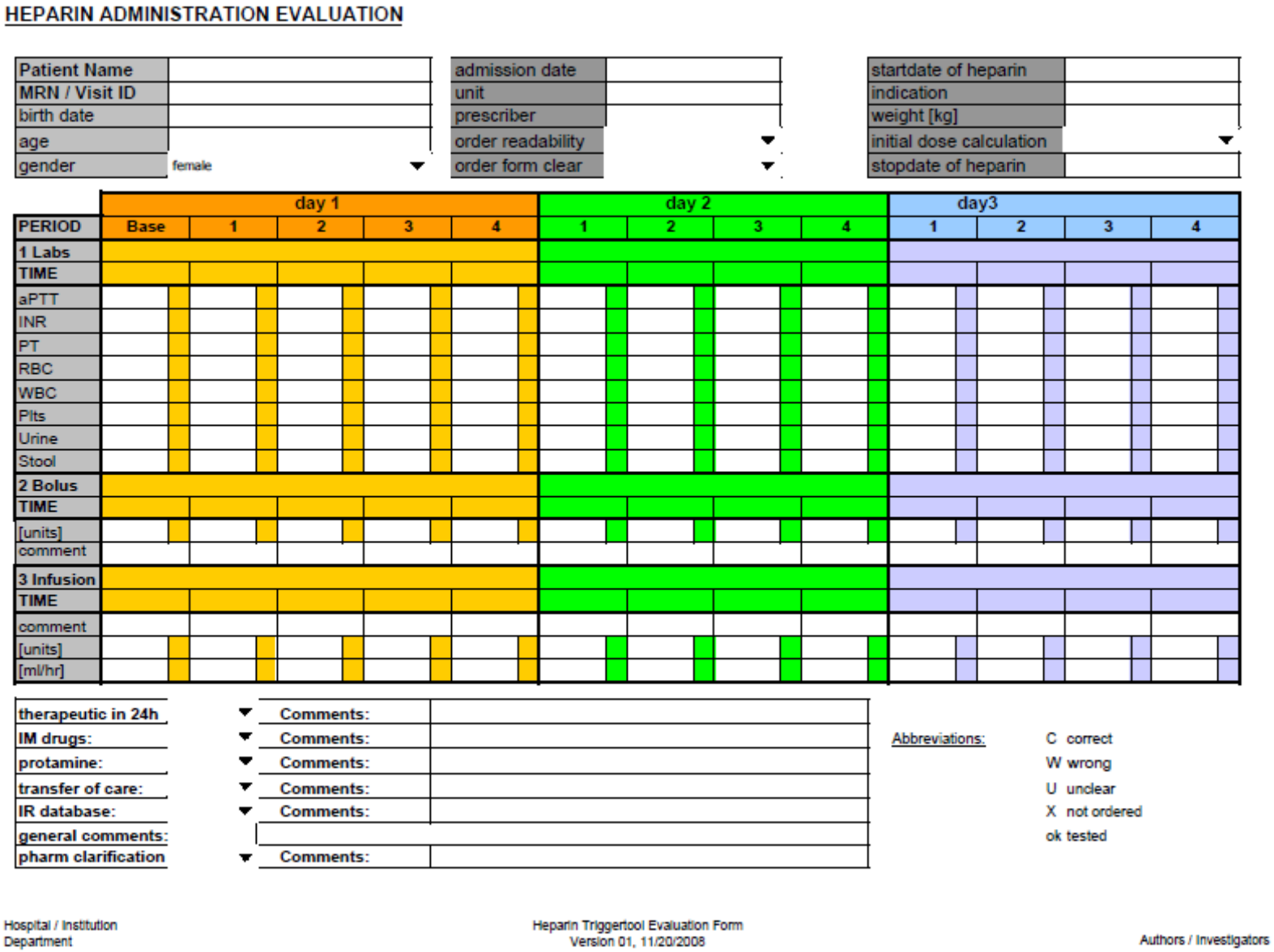
Endpoints	Parameters	2008	2009
Order form use	Order form NOT used	1/19 (6%)	0/20 (0%)
	WRONG order form used	2/19 (11%)	3/20 (15%)
Bolus dosing	calculation NOT according to form	2/8 (25%)	2/5 (40%)
Initial infusion	calculation NOT according to form	8/20 (40%)	7/20 (35%)
Monitoring	aPTT NOT drawn prior to initiation	0/20 (0%)	1/20 (5%)
	inadequate # of lab draws	13/20 (65%)	4/20 (20%)
	excess # of lab draws	---	8/20 (40%)
	at least one missing or delayed lab draw	18/20 (90%)	17/20 (85%)
	NOT correctly timed lab draws (i.e. not within 6-8 hrs of dose initiation /adjustment)	36/82 (44%)	50/128 (39%)
	NOT therapeutic in 24 hours	---	5/20 (25%)
Dose adjustments	Inappropriate dose adjustments in response to aPTT	36/82 (44%)	49/128 (38%)

Additional findings allowed drawing conclusions on the following aspects of UFH therapy:

- Off-label use of UFH
- Execution of the double-check by nursing
- Consistency of patient information (e.g., weight) in different hospital systems containing individual patient information
- The necessity of clarifying physician's orders by pharmacy
- The use of antidotes.

The completion of the manual UFH trigger tool form necessitated 20 minutes per patient on average, executed by a pharmacist with clinical experience.

Figure 3: Manual UFH trigger tool for adult inpatients



HEPARIN ADMINISTRATION EVALUATION

Patient Name		admission date		startdate of heparin	
MRN / Visit ID		unit		indication	
birth date		prescriber		weight [kg]	
age		order readability		initial dose calculation	
gender	female	order form clear		stopdate of heparin	

	day 1					day 2				day3			
PERIOD	Base	1	2	3	4	1	2	3	4	1	2	3	4
1 Labs													
TIME													
aPTT													
INR													
PT													
RBC													
WBC													
Plts													
Urine													
Stool													
2 Bolus													
TIME													
[units]													
comment													
3 Infusion													
TIME													
comment													
[units]													
[ml/hr]													

therapeutic in 24h	Comments:	
IM drugs:	Comments:	
protamine:	Comments:	
transfer of care:	Comments:	
IR database:	Comments:	
general comments:		
pharm clarification	Comments:	

Abbreviations:
C correct
W wrong
U unclear
X not ordered
ok tested

Hospital / Institution
Department

Heparin Triggertool Evaluation Form
Version 01, 11/20/2008

Authors / Investigators

Scroll-down options:

Gender	female
	male
	other
Order readability	good
	acceptable
	bad
Order form clear	yes
	no
Initial dose calculation	weight-based
	aPTT-based
	other
Therapeutic in 24 hours	yes
	no
	unclear
Use of protamine	yes
	no
	unclear
Transfer to a higher level of care	yes
	yes, other reason
	no
Incident report registered	yes
	yes, other reason
	no
Interactions (Drug-drug or food-drug)	yes
	no
	unclear
Pharmacy intervention	yes
	yes, other reason
	no

DISCUSSION

The Institute for Safe Medication Practices considers heparin to be one of the "high alert medications".[110] Intravenous heparin has a narrow therapeutic window, where supratherapeutic doses can lead to severe bleeding complications and subtherapeutic doses to inadequate anticoagulation. It is therefore important to ensure adequate prescribing by using the correct order form, correct dispensing and administration technique, timely monitoring, adequate response time to lab results and appropriate dosage titration.
The trigger tool technology is considered an efficient and effective approach to proactive medication safety assessment.[34] For this pilot and the subsequent follow-up medication use evaluation, a one-page trigger tool form was devised, containing 19 indicators addressing quality and safety aspects of heparin therapy.
The current literature offers a variety of suggested indicators. However, many of them are not validated and might not account for institution-specific structures and processes, which should also be considered.

Although we did include only 20 randomly selected patients in a once-yearly assessment, we were able to identify critical aspects of UFH therapy involving different steps of the medication use process. Problems involving drug prescribing, dispensing by nursing, administration, monitoring and dose adjustment were discovered. As per Bates et al. the process-steps of prescribing and administration are most often affected by errors in medication use, with 39% and 38%, respectively.[123] However, the trigger tool seemed less suited for the detection of problems in the field of transcribing / documenting and dispensing by pharmacy. Because those process steps are affected by errors in 12% and 11% of the cases, more emphasis on those aspects might be sensible for future medication use evaluations.[123]
The evaluation of one patient treated with UFH required approximately 20 minutes and allowed for the identification of areas for improvement.

A prerequisite for the execution of a comprehensive and efficient trigger tool study is the access to all relevant patient information. The information might be fragmented, necessitating access to a variety of databases. Consequently, an electronic database containing all patient information in one place might accelerate the data collection process.[186;197]

For future investigations, additional questions should be considered, specifically addressing the following stages of the medication use process: dispensing by pharmacy, and documentation. As recommended in a previous study, it might also be beneficial to investigate inpatient incident reports as an additional source for medication safety information.[34;133]
Focusing on transfer of care situations might also increase drug safety: if a drug therapy is continued in the outpatient setting after discharge, individual patient education should be an aspect on the trigger tool form.[52] The intensity of clinical pharmacy services might be a marker for quality of medication therapy.[57]

Although indicators have proved to be an efficient tool for medication use evaluation with limited resources, investigators need to be aware, that the trigger tool approach has certain inherent limitations: the small sample size in order to limit resources as well as the fact that the time restricted investigation reflects only a snapshot in time of an institution's drug therapy management.

CONCLUSION

A manual trigger tool form, developed based on expert consensus, was an efficient tool for the assessment of IV heparin use and a promising instrument for the supervision of improvement projects. For a comprehensive monitoring of medication safety, indicators should address all aspects of the medication use process. Additional sources for information on medication use, like incident reporting, should be considered.

In addition to the manual UFH trigger tool, a variety of manual trigger tool forms, addressing different drugs and medication use processes, were developed, piloted and evaluated. They are displayed in Appendix 1 to chapter 4.

APPENDIX 1 TO CHAPTER 4: Examples of trigger tool forms

Pediatric inpatient heparin therapy: manual trigger tool for data collection

HEPARIN ADMINISTRATION EVALUATION

Patient Name		admission date		startdate of heparin	
MRN		unit		indication	
Visit ID		prescriber		weight [kg]	
birth date		discharge date		Creatinine CL	
age		length of stay		initial dose calculation	
gender	female			stopdate of heparin	

	day 1					day 2				day3			
PERIOD	Base	1	2	3	4	1	2	3	4	1	2	3	4
1 Labs													
TIME													
aPTT													
INR													
PT													
RBC													
WBC													
Plts													
Urine													
Stool													
2 Bolus													
TIME													
[units]													
comment													
3 Infusion													
TIME													
comment													
[units]													
[ml/hr]													
comment													

therapeutic in 24h	Comments:		
IM drugs:	Comments:		
protamine:	Comments:		
transfer of care:	Comments:		
IR database:	Comments:		
general comments:			

Abbreviations:

C correct
W wrong
U unclear
X not ordered
ok tested

Hospital / Institution

Heparin Triggertool Evaluation Form
Version 01, 11/20/2008

Authors / Investigators

Scroll-down options:

gender	female
	male
	other
Order readability	good
	acceptable
	bad
Order form clear	yes
	no
Initial dose calculation	weight-based
	aPTT-based
	other
Use of protamine	yes
	no
	unclear
Transfer to a higher level of care	yes
	yes, other reason
	no
Incident report registered	yes
	yes, other reason
	no
Interactions (Drug-drug or food-drug)	yes
	no
	unclear

Adult inpatient oral anticoagulant therapy: template for data collection

Anticoagulation Medication Use Evaluation - Overview Template for Data Collection

☐ Marcoumar
☐ Warfarin
Monitoring
INPATIENT

	Patient	1	2	3	4	5	6	7	8	9	10
	Visit ID										
Demogr.	gender										
	age										
	ethnicity										
Baseline	indication										
	INR										
	PT										
	aPTT										
	platelets										
	RBC										
	WBC										
	hepatic function										
	stool										
Inpatient	goal INR										
	goal INR ok for indication										
	INR daily	*x/x days*									
	dose adjusted to INR daily	*x/x days*									
	warfarin stopped if INR>+0.3										
	INRs in therapeutic range	*x/x days*									
	time to therapeutic range										
	other labs? (stool etc.)										
	hospital diet appropriate										
	concomitant heparin										
	potential drug interactions*										
	manifest drug interactions										
	bleeding events										
	antidote administration										
	IR report / event note										
	other adverse events										
Discharge	therapeutic INR achieved										
	discharge teaching										
	patient warfarin card										
	follow-up appointment										
	PCP information										

* according the list in the actual "Physician's desk reference"

Hospital / Institution Version 02 / 12/05/2010 Author / Investigator

Adult inpatient oral anticoagulant therapy: template for data overview and analysis

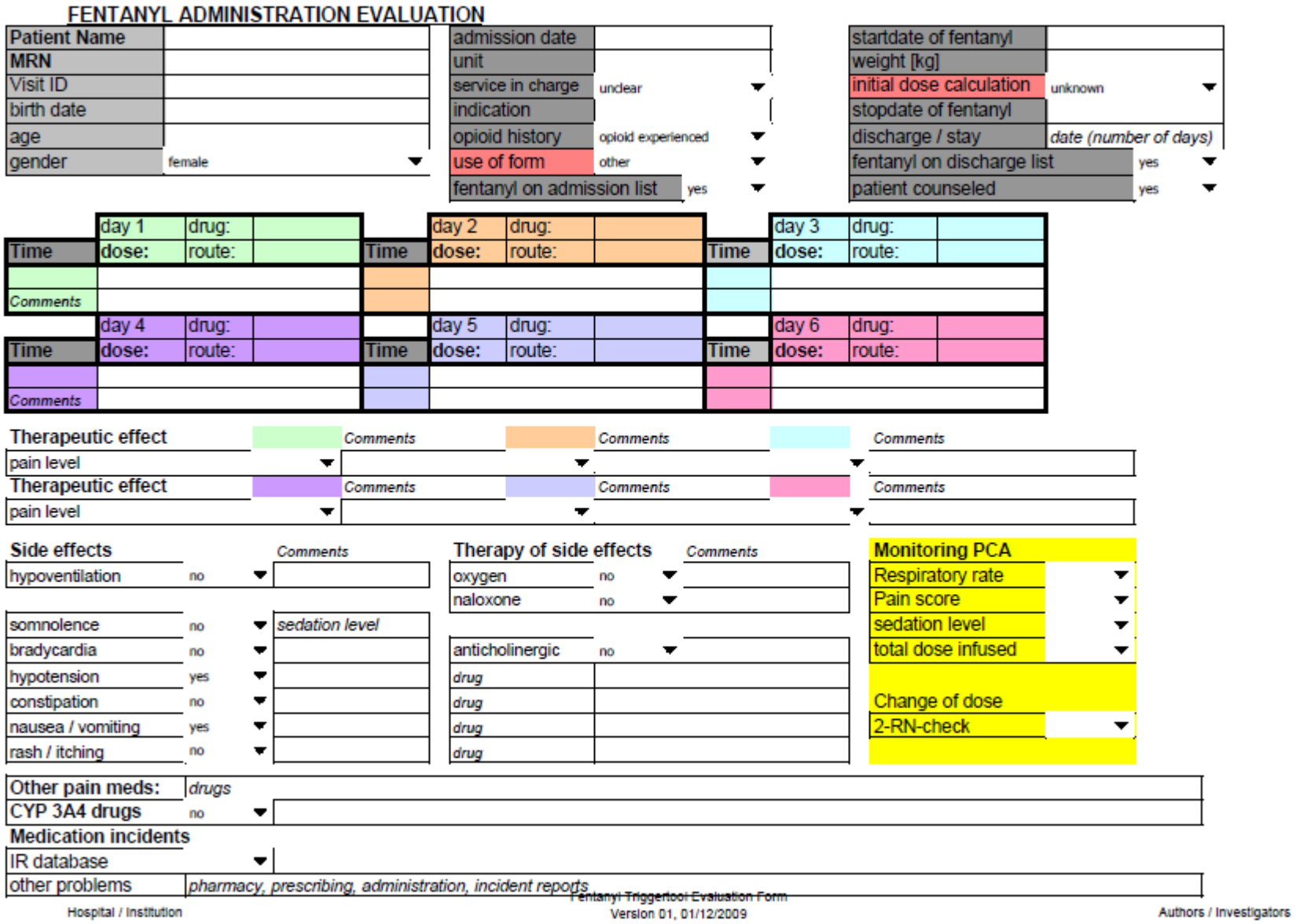
Month: _____ Year: _____

❒ Marcoumar ❒ Warfarin

DEMOGRAPHICS								INITIATION							THERAPY / MONITORING														DISCHARGE			
Name	**MRN**	**unit**	**gender**	**age** [years]	**ethnicity known**	**weight known**	**hospital stay** [days]	**drug on admission**	**dose known**	**goal INR known**	**indication**	**goal INR appropriate**	**pharmacy clarification**	**baseline labs done**	**drug treatment days observed**	**days of goal INR**	**days to therapeutic range**	**lab number: INRs**	**lab number: platelets**	**lab number: aPTTs**	**lab number: CBC**	**stool guaiac**	**drug adjustments**	**antidote administered**	**possible interactions**	**actual interactions**	**concomitant heparin**	**IR / event note**	**other problems**	goal INR achieved	teaching	PCP information	follow-up appointment

Hospital / Institution Version 02 / 12/05/2010 Author / Investigator

Adult inpatient fentanyl therapy: template for data collection



FENTANYL ADMINISTRATION EVALUATION

Patient Name		admission date		startdate of fentanyl	
MRN		unit		weight [kg]	
Visit ID		service in charge	unclear	initial dose calculation	unknown
birth date		indication		stopdate of fentanyl	
age		opioid history	opioid experienced	discharge / stay	*date (number of days)*
gender	female	use of form	other	fentanyl on discharge list	yes
		fentanyl on admission list	yes	patient counseled	yes

	day 1	drug:		day 2	drug:		day 3	drug:	
Time	dose:	route:	Time	dose:	route:	Time	dose:	route:	
Comments									
	day 4	drug:		day 5	drug:		day 6	drug:	
Time	dose:	route:	Time	dose:	route:	Time	dose:	route:	
Comments									

Therapeutic effect		*Comments*		*Comments*		*Comments*
pain level						
Therapeutic effect		*Comments*		*Comments*		*Comments*
pain level						

Side effects		*Comments*
hypoventilation	no	
somnolence	no	*sedation level*
bradycardia	no	
hypotension	yes	
constipation	no	
nausea / vomiting	yes	
rash / itching	no	

Therapy of side effects		*Comments*
oxygen	no	
naloxone	no	
anticholinergic	no	
drug		
drug		
drug		
drug		

Monitoring PCA	
Respiratory rate	
Pain score	
sedation level	
total dose infused	
Change of dose	
2-RN-check	

Other pain meds:	*drugs*	
CYP 3A4 drugs	no	
Medication incidents		
IR database		
other problems	*pharmacy, prescribing, administration, incident reports*	

Hospital / Institution

Fentanyl Triggertool Evaluation Form
Version 01, 01/12/2009

Authors / Investigators

Adult inpatient fentanyl therapy: template for data collection continued

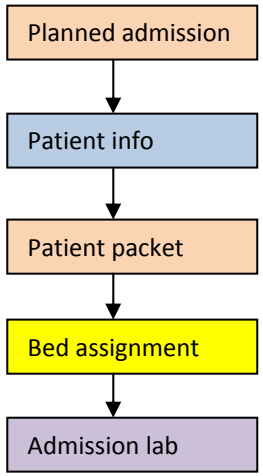
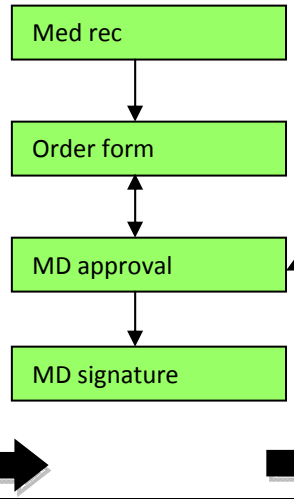
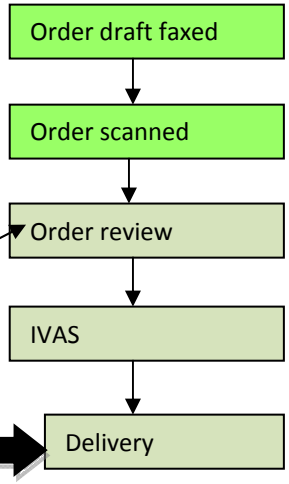
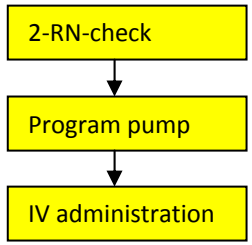
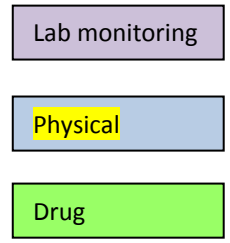
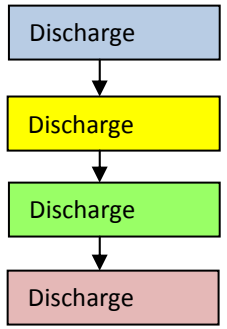
Scroll-down options:

gender	dosage	service in charge	opioid history	use of form	fentanyl on admission list	Initial dose calculation	fentanyl on discharge list	patient counselled	pain level	dose changes	All other questons
female	weight-based	pain service	experienced	correctly	yes	yes	yes	yes	1	yes	yes
male	pain-based	primary care	na!ive	incorrect	no	no	no	no	2	no	no
other	other	both	unknown	not used at all	unclear	unclear	unclear	unclear	… 10	sometimes	unclear
	unknown	unclear		other						unclear	

Adult inpatient fentanyl therapy: template for data overview and analysis

DEMOGRAPHICS						INITIATION					MONITORING																					DISCHARGE	
											patches							concomitant drugs								adverse effects									
Name	**MRN**	**Unit**	**Gender**	**Age** [years]	**Stay** [days]	**opioid experience**	**fentanyl on admission**	**start dose**	pharmacy intervention	**indication**	prescriber	total number	wrong interval	dose increase	dose decrease	removed early	**pain assessment**	laxatives	nausea/vomit	pain PRN	antihistamine	naloxone respiratory	naloxone itch	oxygen	CYP3A4	hypoventilation	somnolence	constipation	nausea/vomit	bradycardia	hypotension	rash/itching	**IR database**	**other problems**	teaching	other problems

Oncology adult: Bone-marrow-transplant / Hematology / Oncology Process Trigger Tool 2009

Service	Admission	Inpatient				Discharge
		Prescribing	Logistics	Administration	Monitoring	
						
Patient coordinator	☐ patient packet on time ☐ face sheet ☐ actual weight info ☐ actual height info ☐ allergy info					☐ follow-up
Nursing	☐ bed assignment on time		☐ pharmacy clarification (chemo start time) ☐ chemo on time ☐ delivery 2-RN-check	☐ premeds ☐ IV access check ☐ 2-RN-check ☐ guardrails used	☐ IV access check ☐ pump check ☐ PRN drugs	☐ teaching
Medicine	☐ prescription (face sheet)	☐ if chemo order form completed by physician, state reason:…… …… ☐ dose accepted ☐ dose rejected	☐ if chemo order form scanned by physician, state reason:…… ……		☐ PRN prescription	☐ final report ☐ PCP info ☐ follow-up

Clinical Pharmacy	☐ orientation on time	☐ med rec performed ☐ allergies ☐ interactions ☐ lab screening done ☐ chemo order form ☐ template available ☐ dose adjustment reason:…… ☐ incompatibilities	☐ order faxed ☐ order scan on time	☐ drug info	☐ supervision: ☐ incompatibilities ☐ ADRs ☐ med errors ☐ meds given ☐ PRN drugs	☐ UCARE report ☐ d/c med list ☐ teaching ☐ info materials ☐ drug list ☐ meds called in
Inpatient Pharmacy (CUDA)			☐ order received on time ☐ order form complete ☐ if clarification, reason: ……		☐ PRN meds on time	
Laboratory	☐ complete admission lab				☐ labs on time	

Depending on the number of voluntary reports submitted and the quantity of patients available for trigger tool evaluation, additional means for medication safety assessment, complementing institution-specific data, might be necessary to obtain a comprehensive impression of a drug's safety profile.
Various institutions all over the world are systematically collecting and analyzing voluntary reports on adverse drug reactions, compiling large numbers of reports.

In the United States, the National Coordinating Council for Medication Error Reporting and Prevention NCCMERP (www.nccmerp.org), the US pharmacopeia (www.medmarx.com) and the FDA (www.fda.gov) are involved in the reporting, discussion and communication about safe medication use, medication errors and error-prone processes. As the NCCMERP states: "*There is no acceptable incidence rate for medication error!".*
The content of the FDA MedWatch system, the central US database for adverse drug events, is accessible to healthcare providers under the "Freedom of Information Act" (http://www.fda.gov/RegulatoryInformation/foi/default.htm).

The WHO's adverse drug event database, maintained by the Uppsala Monitoring Center UMC, is accessible to national pharmacovigilance centers or external inquirers for a charge.

In the following chapters, examples are provided using adverse event report data from the FDA database and the WHO adverse reaction report database.

CHAPTER 5

The FDA extended warning for intravenous haloperidol and torsades de pointes: How should institutions respond?

This chapter has been published in The American Journal of Hospital Pharmacy 2010, volume 5, issue 4.[61]

ABSTRACT

Background:

In September 2007 the Food and Drug Administration (FDA) strengthened label warnings for intravenous (IV) haloperidol regarding QT prolongation (QTP) and torsades de pointes (TdP) in response to adverse event reports. Considering the widespread use of IV haloperidol in the management of acute delirium, the specific FDA recommendation of continuous ECG monitoring in this setting has been associated with some controversy. We reviewed the evidence for the FDA warning and provide a potential medical center response to this warning.

Methods

Cases of intravenous haloperidol-related QTP/TdP were identified by searching Pubmed, Embase, and Scopus databases (01/1823 – 04/2009) and all FDA MedWatch reports of haloperidol-associated adverse events (11/1997-4/2008).

Results

Seventy cases of IV haloperidol-associated QTP and/or TdP were identified. There were 54 reports of TdP; 42 of these events were reportedly preceded by QTP. When post-event QTc data were reported, QTc was prolonged >450msec in 96% of cases. Three patients experienced sudden cardiac arrest. Sixty-eight patients (97%) had additional risk factors for TdP/prolonged QT, most commonly receipt of concomitant proarrhythmic agents. Patients experiencing TdP received a cumulative dose of 5mg to 645mg, patients with QTP alone received a cumulative dose of 2mg to 1540mg.

Conclusions

While administration of IV haloperidol can be associated with QTP/TdP, this complication most often took place in the setting of concomitant risk factors. Importantly, the available data suggest that a total cumulative dose of IV haloperidol of <2mg can safely be administered without ongoing electrocardiographic monitoring in patients without concomitant risk factors.

BACKGROUND

Haloperidol is FDA-approved in the United States for the management of acute and chronic psychotic disorders and widely used in the management of delirium-associated agitation in hospitalized patients.[198] Delirium in the hospital is an acute confusional state that frequently arises from multiple complex factors and may affect up to 30% of hospitalized patients.[199] Although the first step in the management of delirium involves identification and treatment of underlying causes and offering supportive behavioral care, medications may be needed to control severe agitation.[199] Low dose intravenous (IV) haloperidol (i.e., 0.25-0.5mg every 4 hours) is a commonly used medication in this setting as recommended by expert-groups including the Cochrane Collaboration and the American Psychiatric Association.[199;200]

Although injectable haloperidol, a butyrophenone-derived antipsychotic agent pharmacologically related to the piperazine phenothiazines[201], is approved for IV use in many countries (see Table 22), parenteral use is approved only for intramuscular (IM) administration in the United States. Thus, IV administration of the drug in the U.S. is considered an off-label use.[202]

Haloperidol is often preferred over other antipsychotics as a result of its effectiveness, low rate of anticholinergic side effects, familiarity with dosing and usage, and minimal respiratory or sedative properties.[203] Use of the IV route in patients with acute delirium has several advantages over the IM or oral route[204], including rapid onset, immediate bioavailability, and ease and safety of administration.

Prior to September 2007, the package insert for haloperidol alerted health care professionals to the risk of cardiovascular side effects. Based on case reports of potentially fatal cardiac events, the FDA revised the label, warning that the QT prolongation (QTP) and risk of torsades de pointes (TdP) were increased with IV administration of haloperidol or administration of the drug at greater than recommended doses. Unfortunately, neither the "typical" dosing range nor the minimum dose associated with these cardiac side effects were specified in this recommendation.[202]

It is well-established that haloperidol may prolong the QT interval by blocking the repolarizing potassium I_{Kr} current.[205] Although drugs that block the I_{Kr} channel can produce arrhythmia in healthy individuals, additional risk factors, such as underlying heart conditions, electrolyte imbalances (i.e. hypokalemia and hypomagnesemia), concomitant proarrhythmic drug use, and mechanical ventilation may increase this risk.[206] Prolongation of the QT interval has been associated with subsequent malignant cardiac arrhythmias including ventricular fibrillation and TdP.[207] Prolongation of the QT interval is considered the strongest risk factor for TdP, particularly with a baseline QTc >450msec.[206]

Based on the increased risk for QTP and TdP and the case reports of cardiac events, the FDA advisory recommended continuous electrocardiogram (ECG) monitoring in patients receiving IV haloperidol.[202] However, such monitoring may be impractical and costly in hospitalized patients who require low doses of IV haloperidol to manage acute delirium and who are not in telemetry or intensive care units.

The aim of this review was to evaluate the case reports leading to the recent FDA warning for IV haloperidol, specifically focusing on the presence of risk factors for arrhythmias. Based upon the evidence, an additional aim was to provide an institutional response to this warning toward the optimal use of this agent.

Table 22: Package information of officially approved haloperidol IV products

Country	Canada[208]	France[209]	Germany[210]	Great Britain[211]	Italy[212]	Switzerland[72]
Indication	mainly delirium (schizophrenia, other psychosis, short-term management of psychomotor agitation, excitement, violent or dangerously impulsive behavior, vomiting, hiccup)	short term treatment of agitation and aggressiveness during an acute or chronic psychotic episode, vomiting along with antimitotic post-radiotherapy treatment	acute and chronic schizophrenia, psycho-motorical agitation of psychotic genesis	schizophrenia, other psychosis, short-term adjunctive management if psychomotor agitation, violent or dangerous impulsive behavior	resistant forms of psycho-motorical excitement, acute delirious and/or hallucinatory psychosis, chronic psychosis high doses restrictions: syndrome of psycho-motorical excitement, acute delirious and/or hallucinatory psychosis, chronic psychosis	acute schizophrenic episode, mania, vomiting
IV dosing in adults	1 - 2mg every 2 - 4 hours	The use is limited to adult patients and the drug can be administered IM or IV. The IV route is restricted to the treatment of vomiting.	5 - 10mg/day, daily max.: 30(-100)mg	2 - 10mg initially, PRN every 4 to 8 hours, daily max. 18mg	5 - 10mg initially, PRN every hour, daily max. 60mg	5mg PRN every 30 minutes
IV dosing in geriatric care	0.25 to 0.5mg		single dose of 0.5 - 1.5mg, daily max. 5mg	half adult dose	adjust to appropriate dose	0.5mg, than PRN
Risk factors for the development of cardiac adverse events	QT prolonging drugs, diabetes, obesity, hypokalemia, congenital long QT syndrome		QT syndrome, hypokalemia, other electrolyte imbalance, cardiovascular diseases, QT prolongation in the family history	cardiovascular disease, drugs that can prolong the QTc, diabetes, obesity, hypokalemia, congenital long QT syndrome	contraindications: recent cardiac infarction, uncompensated cardiac insufficiency, cardiac arrhythmias, antiarrhythmic drugs, pre-existing QT prolongation, cases of arrhythmia or torsades de pointes in the family history, untreated potassium imbalance, QTc prolonging drugs	QT syndrome, hypokalemia, hypomagnesemia, other electrolyte imbalances, cardiovascular diseases hypothyreosis, QT prolongation in the family history

Monitoring recommendations	electrolytes		ECG monitoring, electrolytes	metabolic parameters	ECG at baseline and regular ECG monitoring, electrolytes	close ECG monitoring, electrolytes
General recommendations	regular reevaluation in long-term use		apply the lowest effective dose	application per mouth is the route of choice	decrease dose if QTc >500msec	switch to PO as soon as possible

Abbreviations: PRN=medication as needed

METHOD

Two search pathways were used to evaluate reports of haloperidol-associated TdP and / or QT prolongation:

1) Literature review

We searched for published literature in humans indexed in Pubmed (1966-April 2009), Embase (1972-April 2009), and Scopus (1823-April 2009) using the search terms *haloperidol* or *Haldol* combined with *intravenous* or *infusion* and at least one of the following terms*: QT prolongation, TdP, torsades de pointes, torsades* with a specific focus on *case reports.* References from the retrieved articles were also reviewed to search for additional case reports.

In addition to cases reported in English journals, several of our reports originated from Japan[213] (translation provided by the FDA), Spain[214] and Germany[215] (translated by the primary author).

2) Search of the FDA database

We reviewed all adverse drug events reported through MedWatch or those submitted by the manufacturer from November 1997-April 2008 through the Freedom of Information Act (FOIA) request. The FDA provided a full-text summary of 5944 reports involving oral, intramuscular and IV use of haloperidol. The FDA data were transferred to a Microsoft Access® database and screened for the key terms *torsade, QT, prolongation, wave.* Incident report number, date of report, age, gender, origin of report, medication name, role of drug as categorized by the FDA (suspect, concomitant, primary suspect, secondary suspect), route, dose, units, duration, symptoms and FDA outcome category (death, life-threatening, hospitalization initial or prolonged, disability, congenital anomaly, required intervention to prevent permanent damage, other) were recorded. Only those reports in which IV haloperidol was considered by the reporter to be the primary causative agent for the adverse event were reviewed. Available information included diagnosis, laboratory parameters, QTc measurement, cardiac symptoms, outcomes and a description of recovery. No peer review was applied to the MedWatch reports and the data reported in this publication reflect the original information from the FDA MedWatch database.

Baseline QTc was either the value defined as such in the original report or the lowest QTc reported.

Haloperidol doses administered were defined as cumulative dose at event, encompassing all doses administered during the hospital stay until the occurrence of the adverse cardiac event.
The drugs listed in the case reports were assessed for proarrhythmic potential using two references: the individual package insert and the website of the Arizona Center for Education and Research on Therapeutics.[216]
The drugs were only considered proarrhythmic when the 2 resources were in agreement.

Duplicates and/or previously published cases, as well as reports involving adverse cardiac effects not associated with QTP or TdP, were identified and excluded.
In their advisory, the FDA does not state the exact origin of the reports, their specific search strategy to identify haloperidol-associated adverse events, or the role IV haloperidol played in the individual events included in the extended warning. Consequently, the number of events identified in this review may differ from that published in the FDA extended warning.

RESULTS

A total of 70 reported cases of IV haloperidol associated TdP and/or QTP were identified. Of these 70, 41 were identified through the Pubmed/Embase/Scopus review, while an additional 29 cases were identified through the FDA database search.
Of the 29 cases in the FDA database, 21 were reported by health care professionals and 8 by manufacturers.
Thirty-five publications described cases originating from the US. Three cases took place in Japan and 1 case each in Canada, Germany and Spain. Several cases in the MedWatch database were reported outside the US: one case each originated from Austria, Canada, France, Japan, Spain, Switzerland and the UK. A summary of the published case reports is displayed in Table 23 and the FDA cases are summarized in Table 24.
Of the 70 cases, 54 cases of TdP were reported. The remaining 16/70 cases involved cases of QTP, 9 of which did not progress to TdP and 7 of which the progression to TdP was unclear. Of note, 42/54 of the cases of TdP were reported as preceded by documented QTP. Presence of QTP was unknown in the other 12 original reports. Three out of 70 patients experienced sudden cardiac arrest, one of which was fatal. One arrest was preceded by TdP and 2 by QTP.

The patient age ranged from 18-86 years. Of note, 17 patients experiencing TdP and/or QTP were < 40 years old, and 2 of those patients were < 30 years old.
Haloperidol-associated QTP and/or TdP were observed in 27 female and 42 male patients; the gender was not stated in one report. Of the 54 patients experiencing TdP (with or without report of previous QTP), 22 were female and 31 were male (1 gender unknown).
Sixty-eight of 70 patients were determined to have associated risk factors[217] for QTP/TdP (see Table 25). The circumstances of the remaining 2 patients were not described in sufficient detail to identify associated risk factors.
Overall, 32 patients had underlying heart conditions. Electrolyte imbalances, including hypokalemia, hypomagnesemia, and hypocalcaemia, were present in 17 patients. At least 39 patients were receiving potentially proarrhythmic agents (1-8 proarrhythmic drugs per patient) in addition to IV haloperidol. At least 23 patients were receiving additional drugs with a potential for other cardiac adverse events than QTP and TdP.
A wide range of other disease states previously reported to be associated with QTP[217] were identified in these patients: asthma (5 patients), diabetes (5 patients), obesity (3 patients), impaired renal and/or liver function (3 patients each), HIV (2 patients); COPD, pancreatitis and hypothyroidism (1 patient each). Twenty two patients had a history of substance abuse (alcohol and/or drugs), and 4 patients were smokers.
The administered doses of IV haloperidol varied widely. Considering that information regarding the maximal daily dose was missing in 22 reports and ambiguous in another 20 cases, the results have been presented using cumulative IV haloperidol doses. Patients experiencing TdP without preceding QTP received a cumulative dose (= total dose at event) ranging from 5mg to 645mg. Patients with both confirmed QTP and TdP were administered a cumulative dose of 2mg to 1700mg. Patients who experienced QTP without TdP received a cumulative dose of 2mg to 1540mg of IV haloperidol.
Sudden cardiac arrest following administration of IV haloperidol was observed in cumulative doses ranging from 6mg to 35mg. The cardiac arrest leading to a fatal outcome was preceded by an administration of at least 6mg of IV haloperidol. Overall, 14 out of 70 patients received cumulative doses of ≤10mg IV haloperidol.
The time from administration to documentation of QTP and/or TdP ranged from immediately post administration to 8 hours after administration of the last dose of IV haloperidol.
Baseline QTc was known in 44 patients. Baseline QTc was >450msec in 18 of these 44 patients.
The change from baseline QTc varied widely from 20msec to 286msec; 36 patients demonstrated a prolongation of >50msec.

In those patients with reported haloperidol associated QTP, 25 patients demonstrated a QTc >600msec and 38 patients >520msec.[206] Of the cases with known specific QTc values, the QTc was prolonged >450msec in 48 out of 50 cases. The lowest reported QTc leading to TdP was 413msec.

Twenty patients were reported as having a "normalization of QTc" (as defined by the original reports) within several hours to 8 days; minimal QTP was reported as persisting in 2 patients. The specifics of the other patients were unknown, although 25 patients were categorized as "recovered", 13 were stated as having an uneventful remainder of hospitalization, and 5 patients were discharged to a rehabilitation facility or a nursing home.

Table 23: Summary of case reports of intravenous haloperidol-associated QTP/TdP published in Pubmed, Embase and/or Scopus (1823 – 04/2009)

Case	Source	Date	Age	Gender	Drugs pro-arrhyth.	Venti-lated	Max. daily dose [mg]	Total dose at event [mg]	Time to event	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	ECG normalization *Outcome*
1	[218]	1991	56	m	no	yes	1200	≥1540	NR	yes	584 (400)	184	NR	NR *uneventful*
2	[215]	1992	36	m	yes	no	≥11.5	≥11.5	20 hrs after start	yes	714 (428)* *estimated	286	yes	QTc normalization (440 msec) *NR*
3	[219]	1993	39	f	yes	yes	NR	580	max. QTc 72 hrs after start	yes	650 (420)	230	yes	QTc normalization after 6 d *uneventful*
4	[219]	1993	19	f	yes	no	170	≥170	max. QT 12 hrs after start	yes	600 (480)	120	yes	QTc normalization after 8 d *uneventful*
5	[219]	1993	63	f	yes	no	NR	489	max. QT 48 hrs after start	yes	670 (520)	150	yes	QTc normalization after 8 d *uneventful*
6	[219]	1993	74	f	yes	yes	NR	10	NR	no	430 (410)	20	yes	QTc unchanged after 8 d *uneventful*
7	[220]	1993	39	m	yes	yes	NR	> 490	NR	yes	457 (348)	109	yes	QTc normalization within 2 to 3 d, no further TdP *NR*
8	[220]	1993	61	m	yes	yes	115	≥211	NR	yes	500 (390)	110	NR	QTc normalization within 2 d *death*
9	[220]	1993	48	m	yes	yes	825	≥825	NR	yes	538 (441)	97	NR	QTc normalization in 3 d *rehabilitation*

Case	Source	Date	Age	Gender	Drugs pro-arrhyth.	Venti-lated	Max. daily dose [mg]	Total dose at event [mg]	Time to event	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	ECG normalization *Outcome*
10	[221]	1994	23	f	yes	yes	120	300	12 hrs after dose increase	yes	NR (550)	NR	yes	NR *uneventful, extubation after 5 d discharge after 10 d*
11	[221]	1994	28	m	yes	yes	300	>300	24 hrs after dose increase	yes	NR (>520)	NR	yes	no recurrence of arrhythmia *patient death (multi-organ failure)*
12	[222]	1995	65	m	yes	NR	230	≥410	worsening from d 2 to d 5	yes	594 (490)	104	yes	QTc normalization (406 msec) *no cardiac problems at discharge*
13	[222]	1995	65	f	yes	NR	500	≥980	after the last 60mg	yes	628 (403)	225	yes	QTc normalization (<400 msec), recurrence with oral haloperidol *rehabilitation*
14	[222]	1995	76	f	yes	NR	≥21	≥26	d 2 after several boluses	yes	670 (450)	220	yes	QTc normalization within several d (412 msec) *rehabilitation*
15	[223]	1994	59	m	NR	yes	865	≥1013	NR	yes	640 (480)	160	NR	QTc normalization in 24 hrs *survived*
16	[224]	1995	76	f	yes	no	NR	44.5 plus 1 PO	15 min	yes	670 (409)	261	yes	ECG normalized the next morning, *no further events*
17	[224]	1995	49	m	yes	no	NR	1150 plus 20 IM	45 min	yes	648 (380)	268	yes	QTc normalization in 24 hrs *anoxic brain insult / rehabilitation*

Case	Source	Date	Age	Gender	Drugs pro-arrhyth.	Venti-lated	Max. daily dose [mg]	Total dose at event [mg]	Time to event	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	ECG normalization *Outcome*
18	[224]	1995	65	f	yes	no	600	965	30 min	yes	628 (403)	225	yes	QTc normalization in 2 d, 3 more episodes of TdP in 3 hrs, no recurrence with further haloperidol, *NR*
19	[225]	1995	42	m	yes	no	28	28	20 min	yes	610 (533)	77	yes	QTc normalization in 5 d *uneventful, ECG normal*
20	[225]	1995	39	m	yes	no	45	45	5 min	yes	654 (NR)	NR	yes	QTc normalization after 24 hrs *uneventful*
21	[213]	1997	56	f	no	no	10	10	shortly after	NR	NR (NR)	NR	yes	TdP resolved after 8 hrs *NR*
22	[213]	1997	82	f	NR	no	10	10	shortly after	yes	680 (NR)	NR	yes	QTc normalization on d 6 after admission (470 msec) *NR*
23	[213]	1997	35	m	NR	no	NR	90	after 20mg	yes	520 (NR)	NR	yes	TdP disappeared 12 hrs later *NR*

Case	Source	Date	Age	Gender	Drugs pro-arrhyth.	Venti-lated	Max. daily dose [mg]	Total dose at event [mg]	Time to event	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	ECG normalization *Outcome*
24	[207;226]	1998	45	m	NR	yes#	NR	9	203 min	yes	638 (560)	78	yes	NR *overall survival 100%, significantly prolonged hospital stay*
25	[207;226]	1998	64	f	NR		NR	115	220 min	yes	605 (424)	181	yes	
26	[207;226]	1998	75	f	NR		NR	85	60 min	yes	567 (508)	59	yes	
27	[207;226]	1998	71	f	NR		NR	55	120 min	paced	paced	paced	yes	
28	[207;226]	1998	58	f	NR		NR	75	38 min	yes	657 (542)	115	yes	
29	[207;226]	1998	40	m	NR		NR	35	15 min	yes	679 (475)	204	yes	
30	[207;226]	1998	71	m	NR		NR	70	58 min	yes	521 (478)	43	yes	
31	[207;226]	1998	47	m	NR		400	400	79 min	yes	574 (444)	130	yes	
32	[227]	1999	41	f	yes	yes	320	915	55 min	yes	610 (426)	184	yes	QTc normalization after 5 d *uneventful*
33	[227]	1999	31	m	yes	yes	480	1700	40 min	yes	599 (491)	108	yes	QTc normalized in 4 d *NR*
34	[228]	2000	64	f	yes	yes	175	175	NR	no	413 (418)	(-5)	yes	QTc remained unchanged *uneventful*
35	[205]	2000	75	m	no	NR	>2	>2	NR	yes	615 (435)	180	no	QTc normalization in 48 hrs *uneventful*

Case	Source	Date	Age	Gender	Drugs pro-arrhyth.	Venti-lated	Max. daily dose [mg]	Total dose at event [mg]	Time to event	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	ECG normalization *Outcome*
36	[205]	2000	68	m	yes	yes	>2	>2	NR	yes	650 (407)	243	no	QTc normalization after 4 d *uneventful after extubation*
37	[205]	2000	77	m	NR	NR	(4)	2	NR	yes	550 (393)	157	no	QTc normalization in 24 to 36 hrs *NR*
38	[214]	2004	34	m	yes	NR	≥24.5	≥24.5	20 min	yes	560 (420)	140	yes	QTc normalization (440msec) *ECG normal*
39	[229]	2004	58	f	yes	NR	340	1010	NR	yes	533 (460)	73	yes	QTc normalization 7 d later *discharge after 27days*
40	[230]	2008	86	f	yes	no	≥2	≥2	8 hrs after last dose	yes	524 (NR)	probably 79	no	QTc normalization (445 msec) *NR*
41	[231]	2009	74	m	yes	no	2	2	shortly after	yes	NR (579)	NR	yes	pre-existing heart block and fibrillation resolved *nursing home / rehabilitation*

Abbreviations: d=day/s; f=female; hrs=hours; m=male; min=minutes; msec=milliseconds; NR=not reported
Five of 8 patients in this case series received concomitant proarrhythmic drugs. The individual patients were unspecified.

Table 24: Summary of FDA MedWatch reports of intravenous haloperidol-associated QTP/TdP, 11/1997-04/2008

Report	MedWatch identifier	Report date	Age	Gender	Drugs pro-arrh.	Max. daily dose [mg]	Total dose at event [mg]	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	Outcome *Recovery*
1	3122988-1	1998	61	m	no	48	48	yes	NR	NR	yes	intervention *NR*
2	3157827-6	1998	44	f	no	160	160	yes	550 (440)	110	yes	intervention *uneventful*
3	3178715-5	1999	60	m	NR	415	645	yes	NR	NR	yes	life-threatening *QTc normalization in 1 day, no recurrence*
4	3271261-X	1999	56	m	NR	NR	≥20	yes	NR	NR	yes	life-threatening *QTc normalization*
5	3271080-4	1999	35	m	yes	≥7	≥7	NR	NR	NR	yes	NR *event abated after dose stopped / reduced, hospitalization prolonged*
6	3325391-4	1999	55	f	yes	75	≥75	NR	NR	NR	yes	life-threatening *event abated after dose stopped / reduced*
7	3381921-8	1999	52	m	no	320	634	yes	458 (430)	28	yes	death *NA*
8	3483869-7	2000	18	m	no	>200	>310	yes	NR	NR	yes	intervention *no recurrence after haloperidol reinstitution*
9	3516342-8	2000	NR	NR	NR	NR	NR	NR	NR	NR	yes	NR *NR*
10	3516320-9	2000	34	m	yes	≥5	≥5	yes	NR	NR	no	life-threatening *event abated after dose stopped*
11	3552263-2	2000	46	f	yes	NR	97.5	yes	NR	NR	yes	life-threatening *event abated after dose stopped / reduced*
12	3574705-9	2000	78	m	yes	NR	160	yes	603 (453)	50	yes	intervention *event abated after dose stopped / reduced*

Report	MedWatch identifier	Report date	Age	Gender	Drugs pro-arrh.	Max. daily dose [mg]	Total dose at event [mg]	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	Outcome *Recovery*
13	3703871-7	2001	27	m	NR	530	530	yes	NR	NR	yes	death *NA*
14	3724567-1	2001	31	m	yes	≥6	≥6	yes	496 (449)	47	no	life-threatening *ECG returned to baseline*
15	3851984-1	2002	72	f	NR	18	18	NR	NR	NR	yes	hospitalization *NR*
16	3942407-2	2002	51	m	yes	14	14	yes	461 (444)	17	yes	life-threatening *no recurrence*
17	4066580-3	2003	> 60	f	NR	50	50	yes	>600 (480)	>120	no	hospitalization *QTc normalization, patient recovered*
18	4126280-8	2003	47	f	NR	60	180	yes	550 (450)	100	no (bradycardia)	hospitalization, *patient recovered*
19	4150700-6	2003	NR	m	NR	5	5	NR	NR	NR	yes	NR *event abated after dose stopped / reduced*
20	4340092-1	2004	52	m	yes	≥5	≥5	yes	>500 (490)	>10	NR (polymorphous VT)	life-threatening *NR*
21	4714692-0	2005	NR	m	NR	NR	NR	yes	NR	NR	yes	hospitalization *event abated after dose stopped / reduced*
22	4881813-9	2006	NR	m	NR	NR	40	NR	NR	NR	yes	hospitalization *event abated after dose stopped / reduced*
23	4892225-6	2006	NR	f	yes	≥10	>10	yes	493 (300)	193	no	hospitalization, *QTc normalization (403 msec)*
24	4911873-8	2006	69	m	yes	≥6	≥6	NR	NR	NR	yes	cardiac arrest, death *NA*
25	5366448-6	2007	53	m	yes	NR	35	yes	NR	NR	NR	cardiac arrest, life-threatening *patient recovered*

Report	MedWatch identifier	Report date	Age	Gender	Drugs pro-arrh.	Max. daily dose [mg]	Total dose at event [mg]	Prolonged QT	QTc maximal (baseline) [msec]	Change in QTc [msec]	TdP	Outcome *Recovery*
26	5563440-3	2007	58	m	possible	≥5	≥5	yes	NR	NR	yes	life-threatening *event abated after dose stopped / reduced*
27	5642929-2	2008	42	m	yes	165	165	yes	640 (350)	290	yes	death *NA*
28	5697758-0	2008	38	m	yes	NR	620	NR	NR	NR	yes	hospitalization *patient recovered*
29	5254840-X	2008	19	f	possible	15	25	yes	461	NR	NR	cardiac arrest, hospitalization *patient recovered*

Abbreviations: d=day/s; f=female; m=mal; msec=milliseconds, NA=not applicable, NR=not reported

Table 25: Presence of risk factors associated with QTP and/or TdP in the published case reports and the FDA MedWatch database

Risk factor	Patients	
	Number	%
Any risk factor	68/70	97
Unknown	2/70	3
Specific risk factors:		
Electrolyte imbalance	27/68	40
Underlying cardiac disease	32/68	47
Concomitant proarrhythmic agents	39/68	57
Other drugs influencing cardiac function	23/68	34
Baseline QTc > 450 msec (QTc known: 44 patients)	18/68 (18/44)	26 (41)

DISCUSSION

The current review was performed in response to the FDA warning recommending the use of continuous ECG monitoring associated with the administration of intravenous haloperidol.[202] This warning has resulted in substantial dilemmas for health care organizations, additional resource allocation, and increased scrutiny from regulatory agencies. The results of our review reveal that intravenous haloperidol-associated QTP and TdP almost uniformly take place in patients with concomitant risk factors and with cumulative doses ≥2mg. In light of these findings, it is possible that hospitals may be able to administer intravenous haloperidol in patients without risk factors without continuous ECG monitoring. In reviewing these published reports, it is important to note that the FDA identified 28 published cases of haloperidol-associated QTP and TdP, while our review yielded a total of 41 published case reports.

The FDA database included 73 cases of haloperidol-associated TdP in their database. However, these cases included both oral as well as IV administration; using our methodology, we identified 29 additional case reports associated with intravenous haloperidol from this database. Consequently, our review included 41 published case reports and 29 FDA database cases, resulting in the total of 70 patients.

Our review revealed a number of practical findings. First, our summary demonstrated that neither QTP nor TdP has been documented with a cumulative dose of IV haloperidol of <2mg. The majority of patients (80%) received cumulative IV doses ≥10mg. The lowest dose associated with sudden cardiac arrest was 6mg and this took place in a 69 year old male patient. Second, the majority (97%) of our patients had additional risk factors for QTP and/or TdP. Pre-existing heart disease[220;224;228;232], electrolyte imbalance[220;227;232;233], concomitant proarrhythmic drugs[220;224;227;232-234] and mechanical ventilation[220;229] were identified as the most commonly observed risk factors (Table 25). Lastly, in those cases in which the data were reported, baseline QTc was >450msec in 41% of the patients, and 96% had a QTc at the time of the event >450msec. Therefore, we conclude that patients 1) receiving low cumulative doses (<2mg) with 2) no risk factors for prolonged QTc or TdP, and 3) with a normal QTc on baseline ECG can safely be given IV haloperidol in the hospital setting. This dosage range is consistent with the labeling for IV haloperidol dosing in Canada[208] and Germany[210] (see Table 1), where single doses of 0.25mg-1.5mg are recommended for the treatment of delirium or acute agitation in the geriatric population.[208;210]

In a recent Cochrane review, low-dose IV haloperidol (<3mg per day) was concluded to be as safe and effective as atypical antipsychotics in the treatment of acute delirium with respect to extrapyramidal adverse effects.[199]

The American Psychiatric Association recommends an initial IV dose of "1-2mg every 2-4 hours as needed (0.25-0.50mg every 4 hours as needed for elderly patients)," with titration to higher doses for patients who continue to be agitated for the treatment of patients with delirium (issued 1999, updated 2004).[200]

While several expert-groups and investigators currently consider IV haloperidol as an important therapeutic option for treating acute delirium and agitation in the dose range presented above, less consensus exists regarding monitoring requirements.[199;200;235;236]

The American Psychiatric Association recommends IV haloperidol only after a baseline ECG is obtained. These guidelines have not been updated since the release of the FDA extended warning.[200] In their recent review, Morandi et al. support the dosage recommendation of the 1999 American Psychiatric Association's practice guidelines for treatment of delirium[200], i.e. administration of IV haloperidol in single doses of 0.5 to 2mg in elderly patients, however, only after a baseline ECG is obtained.[237] While the package insert of IV haloperidol in France[209] recommends a baseline ECG, Germany[210], Italy[212], and Switzerland's[72] package information states the need for regular ECG monitoring. Guidelines for the treatment of delirium in the intensive care unit published by the American College of Critical Care Medicine and the Society of Critical Care Medicine in collaboration with the American Society of Health-System Pharmacists consider IV haloperidol as the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C). These expert groups recommend that patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol (Grade of recommendation = B).[238]

Nevertheless, continuous ECG monitoring (i.e. telemetry) is expensive, labor-intensive and potentially overutilized.[239;240] Requiring clinicians to place all patients receiving intravenous haloperidol on telemetry is impractical and potentially costly. Mandating telemetry could also lead to unintended harm, i.e. use of a less effective or less safe drug to avoid compliance with the telemetry mandate.

Based on our findings and the current recommendations in the literature, inpatient providers should be thoughtful and deliberate in the use of haloperidol to treat acute delirium with agitation. Patients requiring pharmacologic management of their delirium should be screened for risk factors for QTP and TdP (see Table 22) and a baseline ECG should be obtained prior to haloperidol administration. If significant risk factors exist or the baseline ECG reveals a prolonged QTc, then the patient should receive continuous ECG monitoring. Similarly, if cumulative doses of ≥2mg are needed, the patient should be placed on telemetry.

There are some limitations to our study design. Our findings are based upon previously published case reports or data submitted to the FDA MedWatch. While the content of the FDA's MedWatch database is accessible to the public via the Freedom of Information Act (FOIA), the events are neither categorized nor peer-reviewed upon entry into the database. Consequently, information may be incomplete or inaccurate. In addition, the denominator representing the overall use of IV haloperidol is unknown, thus a rate of event cannot be assigned and the true scope of the problem cannot be determined. Despite these limitations, this summary represents the most comprehensive review of the literature to date, expanding on the analysis performed by the FDA. Of note, in our review of the FDA database, we noted several cases of haloperidol-associated QTP or TdP associated with other routes of administration. Thus, it is unknown whether this complication is any greater with IV versus the IM or PO routes of administration.

CONCLUSION

Although the proarrhythmic potential of haloperidol and other antipsychotics has been well established in the literature, IV haloperidol has been considered relatively safe with respect to this complication from the time of its approval in 1967.[202;218;220;227;228;232-234;241] In reviewing all reported cases of cardiac complications associated with IV haloperidol, as well as the current literature, an association with QTP and TdP is likely. However, the case reports reveal that QTP and TdP generally occur in the setting of concomitant risk factors, and no cases have been reported utilizing a cumulative IV dose of <2mg. It may therefore be safe to administer a cumulative dose of IV haloperidol of <2mg without ECG monitoring in patients without risk factors for QTP. However, ECG monitoring should take place with IV haloperidol doses ≥2mg and/or in those patients with additional risk factors of developing QTP and/or TdP.

Based on the findings of this review complemented by the guidelines of various expert-groups and the official labeling information of different countries, the pharmacy & therapeutics committee of the UCSF Medical Center revised the IV haloperidol policy: Administration of a total dose of <2mg IV haloperidol without concurrent telemetry is allowed in a non-critical care setting in patients without risk factors for QTP and TdP.

CHAPTER 6

The case of IV haloperidol – Does the WHO pharmacovigilance database offer evaluable comparative safety data?

This chapter has been submitted for publication to The International Journal of Clinical Pharmacy 2010, in March 2011

ABSTRACT

Background

In September 2007, the United States Food and Drug Administration (FDA) strengthened label warnings for intravenous (IV) haloperidol. Based on adverse event reports, continuous telemetry was recommended due to an increased risk of QT prolongation (QTP) and torsades de pointes (TdP).

Considering that IV haloperidol is commonly used as a first line treatment for acute delirium, the extended warning has caused widespread uncertainty among health care professionals and further exacerbated by the threatened withdrawal of IV haloperidol from the market in Europe.

The aim of this study is to critically evaluate the WHO adverse drug reaction (ADR) reports of QTP, TdP and/or cardiac events involving IV haloperidol specifically compared to other routes of haloperidol administration and also to other antipsychotic agents (olanzapine, quetiapine).

Method

All WHO reports (1972- January 2010) of cardiac ADRs associated with haloperidol, quetiapine and olanzapine were evaluated, including dose, route of administration and known patient risk factors. Reporting odds ratios (RORs) for the 3 antipsychotics were calculated.

Results

The absolute number of ADR reports regarding QTP, TdP and/or cardiac arrest were as follows: haloperidol (365 cases), olanzapine (489 cases) and quetiapine (520 cases). However, reporting rates of haloperidol did not increase over the last two decades, and 32% of the haloperidol cases involved PO, 16.4% IM and 22.7% IV administration.

The difference of the RORs of haloperidol and quetiapine were not statistically significant. Olanzapine was associated with a slightly lower ROR when compared with quetiapine and haloperidol.

Conclusion

While regulatory agencies recommend caution regarding the use of intravenous haloperidol, review of the WHO ADR database does not reveal that the intravenous route is any more likely to be associated with QTP, TdP and/or cardiac arrest than oral or intramuscular. Furthermore, our results do not demonstrate any additional risk associated with haloperidol when compared with alternative agents. Since pharmacovigilance data does not routinely include a denominator regarding frequency of use, it should only be used for trending. Nonetheless, regulatory agencies are currently advising against the use of IV haloperidol based on pharmacovigilance data.

Transparency regarding the decision-making process of regulatory agencies would be highly desirable from a clinician's point of view. In addition, improved pharmacovigilance approaches are needed to more accurately recommend changes in policy regarding the safe, effective use of medicines.

BACKGROUND

In September 2007, in response to adverse event reports, the United States Food and Drug Administration (FDA) strengthened label warnings for intravenous (IV) haloperidol. The label change included a warning that the risk of QT prolongation (QTP) and torsades de pointes (TdP) might be increased with IV administration or administration of more than recommended doses. Unfortunately, specific dosing recommendations and information regarding potential alternatives were not included in the warning.[202]

Although the American Psychiatric Association and the Society of Critical Care Medicine recommend haloperidol, a first-generation-antipsychotic as first-line agent for the treatment of delirium[200;238], IV haloperidol has always been off-label in the United States[198]. The IV route was approved in several other countries including Switzerland[72], Canada[208], France[209], Germany[210], Great Britain[211], and Italy[212] until June 2010, when the current controversy resulted in removal of this route from the labeling. While the package insert for IV haloperidol prior to September 2007 alerted healthcare professionals to the risk of cardiovascular side effects, recommendations regarding monitoring were inconclusive.[61] However, in May 2010, the Pharmacy and Therapeutics committee of the German Physicians' Association (AkdÄ) followed the FDA recommendation and sent out a drug safety letter regarding the use of IV haloperidol. According to the revised manufacturer information, continuous electrocardiogram (ECG) monitoring was strongly recommended when administering IV haloperidol.[242]

While the IV administration is not necessarily the route of choice, it is considered an alternative particularly with acute agitation. Oral or intramuscular administration offers additional challenges for patients with acute delirium, particularly in the general ward setting in which continuous ECG monitoring is not feasible.

In a recent systematic review of published case reports on IV haloperidol and the FDA pharmacovigilance database, a dose of less than 2mg of IV haloperidol was considered safe for patients with no pre-existing risk factors for cardiac side effects.[61] However, it is possible that this dose might be too low for highly agitated patients. Consequently, physicians are considering therapeutic alternatives to IV haloperidol.

It is unknown whether the intravenous route of haloperidol is indeed unsafe and whether the route of administration influences the safety profile of haloperidol. Furthermore, it is not known whether other agents used for the treatment of acute agitation and delirium, i.e. quetiapine and olanzapine, are also associated with electrocardiac changes.

The aim of this study was to use the WHO ADR database to 1) assess the relative cardiac safety of the respective routes of administration for haloperidol and 2) compare the safety of haloperidol to the atypical antipsychotics quetiapine and olanzapine.

METHOD

Analysis of the WHO adverse drug reaction database

In 1968 the WHO established the "Program for International Drug Monitoring" with the aim of monitoring, assessing and collecting information from the pharmacovigilance centers of member countries. Since 1978 the Uppsala Monitoring Centre (UMC) has been responsible for the program.[243] The UMC collects cases of suspected adverse drug reactions spontaneously reported by health care professionals, hospitals, lawyers and manufacturers of member countries. Currently, the WHO ADR database contains more than 4 million individual case safety reports (ICSRs). Cases reported in the published literature are not included in the database.[243]

An official search was performed in the WHO ADR database for the drugs haloperidol, quetiapine and olanzapine combined with cardiac adverse drug reactions described with the WHO-ART terms "QT prolonged" (high level term), "torsade de pointes" (preferred term) and / or "cardiac arrest" (excluding: "cardiac arrest neonatal" / preferred term). Reports from 1972 until January 4, 2010 were included, no country restrictions were applied.

The data was obtained in an Excel-sheet showing single case reports in multiple rows. The data was converted by a professional programmer to organize each case report in a single row for optimal searching for trends.

The reporting odds ratio (ROR) of haloperidol is defined as the ratio of the exposure odds among reported cases of haloperidol-associated cardiac adverse reactions to the exposure odds of all the other reported ADRs of haloperidol-induced cardiac ADRs. The ROR of haloperidol in comparison with the ROR of cardiac ADRs of olanzapine and quetiapine was calculated as previously described.[244;245]

RESULTS

Analysis of the WHO adverse drug reaction database

Overall data

During the period from 1972 until January 4, 2010 the UMC received 1374 ICSRs on QTP, TdP and/or cardiac arrest associated with the administration of haloperidol (365 cases), olanzapine (489 cases) or quetiapine (520 cases). The reported cases included 529 males and 605 females; in 240 cases the gender was not provided by the reporter.

The first reports of cardiac ADRs associated with haloperidol, olanzapine and quetiapine dated back to 1972, 1996 and 1995, respectively. The detailed data on the ICSRs overall is displayed in table 26.

The reporting numbers of the study drugs per year are displayed in table 27. Reporting rates of haloperidol did not increase over the last two decades.

The average age of patients with cardiac events associated with the administration of haloperidol was 49 years (S.D. ± 16.2 years), with olanzapine 47 years (S.D. ± 14.5 years) and with quetiapine 45 years (S.D. ± 13.3 years). In 149 case reports (10.8% of the total) the age of the patient was not specified.

Only limited data regarding route of administration and dose was available in the ICRS. The information is displayed in tables 28 – 30. Of the 365 haloperidol reports, 120 cases involved PO administration (32.9%), and 60 IM administration (16.4%), 83 IV administration (22.7%). In 90 cases (24.7%), the route of administration was unknown, in 2 cases (0.5%) “parenteral” was indicated. Daily doses of haloperidol ranged from 0.6 mg to 675 mg, with an average daily dose of 49 mg (SD +/-113 mg, median 15 mg).

Overall nine patients with a reported cardiac ADR (all in relation with QTP and/or TDP) received haloperidol doses <2mg/day. The lowest dose associated with a fatal event was 1mg. (see table 31)

Of the 489 olanzapine reports, only in 75 cases (15.3%) was the route of administration, dose and frequency of administration available to allow for calculation of the daily dose. Daily doses administered ranged from 1.25 mg to 700 mg, with an average daily dose of 25 mg. (SD +/-72 mg, median 10 mg).

The quetiapine reports contained 89/520 (17.1%) detailed case descriptions. Daily administered doses ranged from 25 mg to 4500 mg, with an average daily dose of 623 mg (SD +/-760 mg, median 400 mg). One case, a non-fatal suicide attempt with 30,000 mg of quetiapine, was excluded from the calculation.

Table 26: Details of case reports in the WHO ADR database

	Total reports N = 1374	**Haloperidol** N = 365	**Olanzapine** N = 489	**Quetiapine** N = 520
Age (mean +/- SD)	47 +/- 14.5	49 +/- 16.2	47 +/- 14.5	45 +/- 13
Age unknown (%)	149 (10.8%)	40 (11%)	47 (9.6%)	62 (11.9%)
N ≥ 65 years (%)	212 (15.4%)	78 (21.4%)	78 (17.6%)	56 (12.2%)
Sex male (%)	529 (46.6%)	200 (58.5%)	182 (47.2%)	147 (36.2%)
Sex female (%)	605 (53.4%)	142 (41.5%)	204 (52.8%)	259 (63.8%)
Sex unknown	240	23	103	114
Number of reports with available route, daily dose		100	75	89
PO (%)		120 (32.9%)	70 (93%)	89 (100%)
IV (%)		83 (22.7%)	NA	NA
IM (%)		60 (16.4%)	5 (7%)	NA
Parenteral unspecified		2 (0.5%)	NA	NA
Unknown		90 (24.7%)	0 (0%)	NA
Outcome fatal	739	155 (42.5% of haloperidol)	276 (54.6% of olanzapine)	308 (59.2% of quetiapine)
male	262	89	93	80
female	279	53	96	130
unknown	198	13	87	98

NA = not applicable (no formulation approved)

Table 27: Number of ADR reports per year and drug

	Haloperidol				**Olanzapine**			**Quetiapine**
Timeframe	**overall**	**PO**	**IV**	**IM**	**overall**	**PO**	**IM**	**PO**
1972 - 1979	13 (6.5%)	8 (12.3%)	1 (1.5%)	4 (11.1%)	NA	NA	NA	NA
1980 - 1989	33 (16.5%)	16 (24.6%)	3 (4.6%)	7 (19.4%)	NA	NA	NA	NA
1990 - 1999	78 (39%)	19 (29.2%)	32 (49.2%)	17 (47.2%)	62 (31.6%)	29 (25.9%)	0 (0%)	10 (7.4%)
2000 - 2009	76 (38%)	22 (33.8)	29 (44.6%)	8 (22.2%)	134 (68.4%)	83 (74.1%)	5 (100%)	126 (92.6%)

NA = not applicable (no formulation approved)

A total of 743 cases with fatal outcome were reported (54.1%), 4 of these were excluded because they were explicitly reported to be unrelated to cardiac etiology, resulting in a total of 739 cases. In 155 patients the cardiac event was associated with haloperidol (89 males, 53 females, 13 unspecified), doses ranging from 1mg to 530mg; in 276 patients with olanzapine (93 males, 96 females, 87 unspecified), doses ranging from 5mg to 80mg; and in 308 patients with quetiapine (80 males, 130 females, 98 unspecified), doses ranging from 25 to 4500mg. Details on the doses administered are displayed in table 32.
Of the 78 elderly patients whose cardiac events were associated with the administration of haloperidol, 45 died (57.7%). Of the 78 elderly patients whose cardiac events were associated with the administration of olanzapine 53 (67.9%) died, whereas of the 56 elderly patients whose cardiac events where associated with quetiapine 41 (73.2%) died.

Reporting odds ratio

The ROR for the risk of cardiac ADRs associated with the use of any one of the study drugs (haloperidol, olanzapine, quetiapine) compared with cardiac ADRs associated with all other drugs in the WHO database was 3.15 (CI 95%, 2.98 - 3.33). The ROR for haloperidol was 3.66 (CI 95%, 3.30 – 4.07), for olanzapine 2.67 (CI 95%, 2.44 – 2.92) and for quetiapine 3.39 (CI 95%, 3.11 – 3.70) compared to cardiac ADRs following therapy with other drugs. The difference of the ROR between haloperidol and quetiapine was statistically not significant (p>0.05, overlapping confidence intervals). Olanzapine was associated with a slightly lower ROR when compared with quetiapine and haloperidol.

Table 28: Distribution of administered doses of haloperidol associated with adverse cardiac reactions (QTP and/or TdP and/or cardiac arrest), stratified by route of administration

Haloperidol daily dose	**Number of reported cases**		
	PO [n=47]	**IV** [n=23]	**IM** [n=30]
< 2 mg*	4	1	1
2 mg - ≤ 3 mg	11	4	4
> 3 mg - ≤ 5 mg	6	0	5
> 5 mg - ≤ 10 mg	5	3	6
> 10 mg - ≤ 20 mg	8	2	5
> 20 mg - ≤ 50 mg	7	2	4
> 50 mg - ≤ 100 mg	5	4	5
> 100 mg	1	7	0

* route unknown: 3

Table 29: Distribution of administered doses of olanzapine associated with adverse cardiac reactions, stratified by route of administration

Olanzapine daily dose	**Number of case reports**	
	PO [n = 70]	**IV** [n = 5]
≤ 3 mg	4	0
> 3 mg ≤ 5 mg	13	0
> 5 mg ≤ 10 mg	23	2
> 10 mg ≤ 20 mg	18	2
> 20 mg ≤ 50 mg	9	1
> 50 mg ≤ 300 mg	2	0
> 300 mg	1	0

Table 30: Distribution of administered doses of quetiapine associated with adverse cardiac reactions, sorted by route of administration

Quetiapine daily dose	**Number of reported cases**
	PO [n=89]
≤ 100 mg	25
> 100 mg ≤ 200 mg	11
> 200 mg ≤ 300 mg	8
> 300 mg ≤ 400 mg	8
> 400 mg ≤ 500 mg	5
> 500 mg ≤ 600 mg	11
> 600 mg ≤ 700 mg	2
> 700 mg ≤ 800 mg	3
> 800 mg ≤ 900 mg	2
> 900 mg ≤ 1000 mg	3
> 1000 mg ≤ 1200 mg	2
> 1200 mg ≤ 1400 mg	3
> 1400 mg ≤ 1600 mg	1
> 1600 mg ≤ 1800 mg	1
> 1800 mg ≤ 2000 mg	1
> 2000 mg ≤ 5000 mg	2
> 5000 mg ≤ 30,000mg	1

Table 31: Daily doses of Haloperidol, Olanzapine and Quetiapine, overall and with fatal outcome after QTP and/or TdP and/or cardiac arrest

	Haloperidol								Olanzapine						Quetiapine	
	Overall cases [mg]				Cases with fatal outcome [mg]				Overall cases [mg]			Cases with fatal outcome [mg]			Overall cases [mg]	Cases with fatal outcome [mg]
Daily dose	**total**	**PO**	**IV**	**IM**	**total**	**PO**	**IV**	**IM**	**total**	**PO**	**IM**	**total**	**PO**	**IM**	**PO**	**PO**
Lowest	0.6	1	1	1	1	1	1	1	1.25	1.25	10	5	5	10	25	50
Highest	675	500	675	85	530	500	530	85	700	700	20	80	30	20	4500	4500
Mean	49	31	102	26	39	35	81	27	25	25	14	17	13	17	623	928
SD	113	24	179	27	96	101	177	29	72	84	5.5	14	8	6	760	1156
Median	15	12	20	15	10	8	5	15	10	10	10	10	10	20	400	600

Table 32: Case reports of patients treated with <2mg of haloperidol and experiencing QTP, TdP and/or cardiac arrest

Report	Report Date [year]	Origin	Age	Gender	Dose	Frequency	Route	Symptoms	Seriousness	Outcome	Causality	Notifier	Concomittant drugs	Indication for haloperidol	Other illnesses
1	1985	USA	72	Female	1 mg	daily	PO	Cardiac arrest	NR	Died	NR	Other	None reported	NR	CV Disease
2	1986	USA	73	Male	1 mg	daily	IV	Cardiac arrest	Death	Died	NR	Other	None reported	NR	NR
3	1986	USA	37	Male	1 mg	daily	IM	Cardiac arrest	NR	Died	NR	Other	Nalbuphin, phenyltoloxamine, hydrocodone	NR	NR
4	NR	USA	12	Male	1 mg	daily	PO	Cardiac arrest	Death	Died	NR	Other	None reported	NR	NR
5	1999	FIN	75	Female	1 mg	daily	PO	QTP, TdP	NR	Died	Probable	Hospital	Furosemide 160 mg PO, amlodipine 5 mg PO, risperidone 1mg PO, metoprolol 95 mg PO	NR	NR
6	2004	NLD	84	Female	1.5 mg	daily	NR	TdP	Other	Unknown	NR	NR	None reported	NR	NR
7	NR	CHE	92	Female	0.6 mg	daily	NR	QTP, TdP, AV block complete	Life threatening	Recovered	Possible	NR	Amantadine, bisoprolol 2.5 mg, levodopa, benserazide	Restlessness, agitation	Parkinson's, CV Disease
8	2009	CHE	82	Female	1 mg	daily	PO	QTP	Other	NR	NR	Physician	Acetylsalicylic acid 100 mg PO, metoprolol 12.5 mg PO, Calcium gluconate 500 mg PO, Enoxaparin 40 mg	Restlessness, agitation	NR
9	NR	USA	18	Female	1 mg	NR	NR	Cardiac arrest	Death	Died	NR	Physician	Paracetamol PO, diazepam, flurazepam, imipramine	Agitation, stress	Broncho-pneumonia, Hyperpyrexia

AV = atrio-ventricular, CHE = Switzerland, FIN = Finland, CV = cardio vascular, HCl = hydrochloride, IM = intramuscular, IV = intravenous, NLD = The Netherlands, NR = not reported, PO = oral, QTP = QT prolongation, TdP = Torsades de pointes, USA = United States of America

DISCUSSION

In 2007, the FDA strengthened label warnings for IV haloperidol in response to reports on cardiac adverse events. The release of this warning was based on post-marketing pharmacovigilance data.[202]

The request of continuous ECG monitoring, often impractical on non-intensive care units, raised the question among health care professionals if different routes of administration or the use of atypical antipsychotics might be an alternative to IV haloperidol, specifically in treating acute conditions like delirium.[202]

The WHO ADR database is based on spontaneous, voluntary reporting and does not allow a definite quantitative comparison of events due to underreporting influencing the nominator as well as due to the missing denominator of overall use, overall use per route of administration, gender and age. However, it is clear that cardiac adverse events involve a wide variety of doses, different routes of haloperidol administration and other antipsychotics quetiapine and olanzapine.

One limitation with the calculated ROR is that it is not corrected for year of registration and highly dependant on the number and types of cases reported. Furthermore, it is difficult to clearly link cause and effect between the agent and the adverse event. Thus, the ROR simply reflects the comparative reporting behavior regarding different drugs and is quite limited in its ability to reflect actual incident rates.[246] Nevertheless, the difference of the ROR between haloperidol and quetiapine was not statistically significant in our analysis, suggesting no increase in reporting for haloperidol compared to atypical antipsychotics. If one bases conclusions upon spontaneous reporting systems, there is no evidence that haloperidol is more dangerous than other antipsychotics. This notion is further supported by the fact that haloperidol has been marketed much longer than olanzapine and quetiapine, and that there was no increase in reporting for haloperidol over the last two decades.

Haloperidol has never been evaluated in a prospective, controlled trial to evaluate the true incidence of cardiac adverse events associated with the route of administration. Ozeki et al. calculated the relative risk of QTP associated with the administration of various drugs for the treatment of schizophrenia. The administration of 2mg of IV haloperidol resulted in a calculated relative risk of 1.29 compared to 0.99 for 2mg of PO haloperidol. The authors conclude that IV haloperidol is significantly more likely to be associated with QTP compared with the oral route.[247]

Atypical antipsychotics are associated with substantially less EPS when compared with conventional antipsychotics such as haloperidol. Consequently, these agents are commonly used in the management of psychiatric disorders.[248] With this increase in the use of second generation antipsychotics, concerns about efficacy and safety in vulnerable patients (e.g. geriatric patients with dementia) have been raised.[249]
Accordingly, in 2005 the FDA issued a Public Health Advisory warning against the use of atypical antipsychotics in elderly patients with dementia because of the associated increased risk of death.[202]
Only 2 studies directly compare haloperidol with olanzapine, while only 1 study compares haloperidol with quetiapine in the treatment of delirium.[250-252]
Skrobik et al. performed a single-blind, randomized study comparing the efficacy and safety of PO haloperidol and PO olanzapine in 73 critically ill patients with delirium. Fourty-two percent of the patients treated with olanzapine and 35% of the patients treated with PO haloperidol required rescue therapy with IV haloperidol. None of the 73 patients experienced a QTP or other cardiac events.[250]
Sipahimalani et al. conducted a retrospective, nonrandomized study comparing haloperidol and olanzapine in 22 patients with delirium. Significant symptom improvement was observed in 5 patients treated with olanzapine and in 6 patients treated with haloperidol. The only side effects reported were EPS and over-sedation in the haloperidol group.[251]
Schwartz et al. performed a retrospective chart review comparing haloperidol and quetiapine for the treatment of 22 patients with delirium. Satisfactory clinical responses with overall improvements in delirium symptomatic were observed in 10 patients in each group. No cardiac side effects were reported.[252]
While these 3 comparative studies are not adequately powered to detect differences in rare ADRs, they are the only controlled trials that exist.[250;251]

Czekalla et al. summarized the results of 4 controlled randomized clinical trials conducted with 2700 patients and concluded olanzapine is associated with the lowest risk of QTP when compared with other atypical antipsychotics.[253] Another prospective clinical study documented olanzapine-induced QTP, however this prolongation was not statistically significant.[254] In another study QTc prolongation was not observed even after olanzapine overdose.[255] In contrast, in a study performed at the Beer-Sheva Mental Health Center in Israel, a mean prolonged QTc interval of 504.6 ± 7.0msec was observed in 17 patients with no known underlying cardiac diseases, but regularly taking olanzapine.[256]

Like all other atypical antipsychotics olanzapine shows an advantage over haloperidol because of the low risk of EPS.[257] However, the relatively long onset of action of the PO form (from 5 to 8 hours) greatly diminishes its value in emergency cases of delirium.[72]
The finding of Schwartz et al. that quetiapine is a safe and efficacious therapeutic alternative to haloperidol in the treatment of delirium might be worth further investigation[252], especially due to its very low propensity to cause EPS.[249] An interesting characteristic of quetiapine is the relatively short half life (7 hours), which allows for rapid elimination in the case of serious ADRs.[258]
While some experts state that atypical antipsychotics might have a more favorable cardiac safety profile, this benefit has not been clearly established. The Arizona Center for Research and Therapeutics (Arizona CERT) still categorizes haloperidol as a “drug with risk”, while quetiapine is only classified as “drug with possible risk”. Olanzapine is not included on any risk list.[259]
Prescribers should recognize QTP is more likely when treating patients with baseline risk factors.[61] These factors include female sex (71.4%), drug interactions and polypharmacy (44.7%), cardiac disorders (43.1%), overdose (27.0%), electrolyte imbalances (17.0%), congenital Long QT Syndromes (17.1%).[260] Notably 70 patients with antipsychotic-induced TdP were included in this review, and most presented with 2 or more risk factors.[260]

While some authors suggest an increased risk of cardiac events with intravenous haloperidol administration, review of the WHO ADR database does not support this conclusion. From a practical point of view, intravenous administration offers distinct advantages in the inpatient setting. In the absence of controlled trials, oral administration with drops or fast-melt tablets represent a potential option.[61] While obviously more painful compared with intravenous, intramuscular administration is also a possibility.[261]

CONCLUSION

While pharmacovigilance data is substantially limited due to underreporting and the missing denominator pertaining to use, regulatory agencies are using this information to produce medication warnings. Specifically, these data have been used in advising against the use of IV haloperidol in the treatment of acute delirium. The WHO database reveals a greater number of cardiac ADR reports for PO haloperidol when compared with the IV route. Also of note, the number of overall cardiac ADRs involving QTP and/or TdP was greater for quetiapine and olanzapine when compared to haloperidol.

Transparency regarding the decision-making process of regulatory agencies would be highly desirable from a clinician's point of view. Improved pharmacovigilance approaches are needed to more accurately recommend changes in policy regarding the safe, effective use of medicines, including antipsychotics in the treatment of acute delirium.

Accompanying statement

(i) The data on which this work is based were obtained from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

(ii) The information contained in this work is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction.

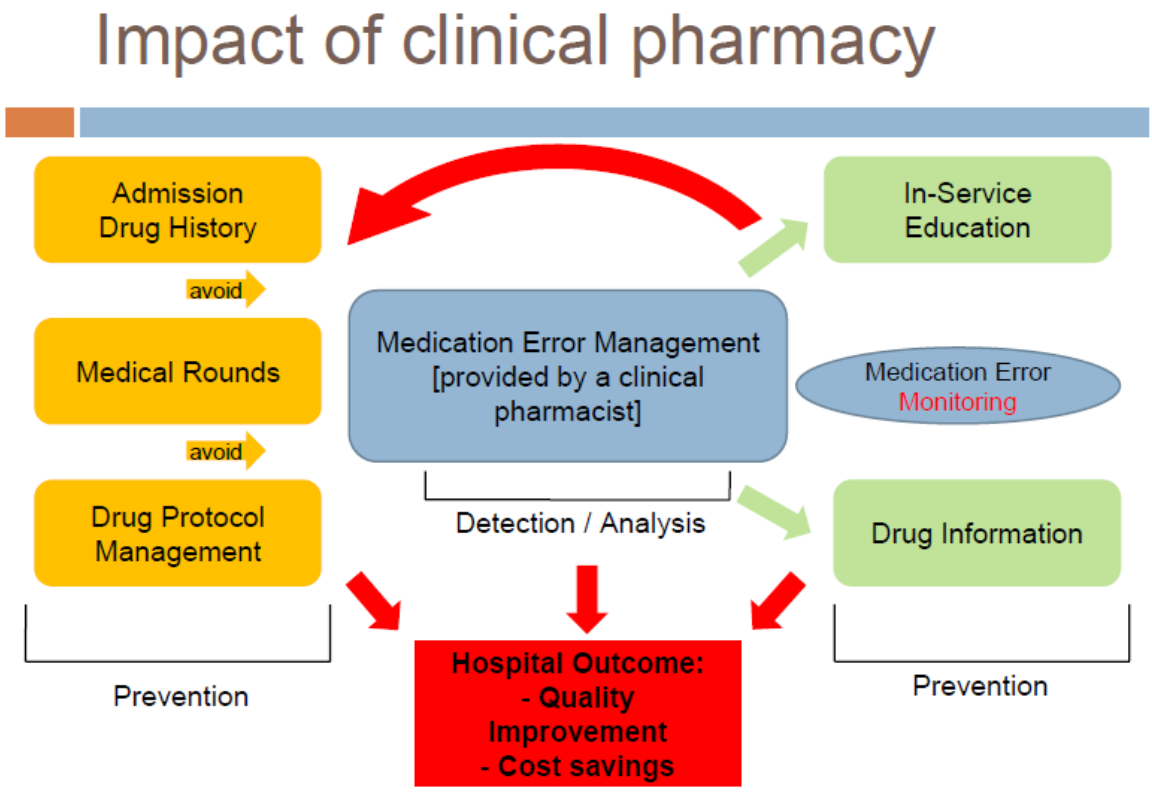
(iii) The information contained in this work does not represent the opinion of the World Health Organization.

SUMMARY AND PERSPECTIVES

Ten years after the publication of “To Err is Human”, patient safety is a significant concern for regulatory agencies and hospitals. Despite this report, patient safety is still lacking and additional efforts are needed to improve health care quality.[7;262] Medication-related harm is among the top reasons for decreased patient safety.[263] Most importantly, more than 60% of the adverse events are considered preventable.[262]

Although adverse drug event reduction is clearly an interdisciplinary approach, the current literature shows that clinical pharmacy services, involving drug information services, clinical research, proactive adverse drug reaction management, medical rounds participation, drug protocol and therapy management, and drug counseling, can improve medication safety significantly (see also Figure 4).[42;57;57]

Figure 4: Clinical pharmacist’ activities improving medication safety



A survey among Swiss hospital pharmacy directors has shown clearly, that the improvement of medication safety through the implementation of clinical pharmacy services is a priority.

Patient-specific medication during transition of care is important to improve individual drug therapy outcomes[21;22;38;41;43;264], however, a more systematic approach should be considered in order to address system failures regarding medication use[45].
While the role of the clinical pharmacist as a medication safety officer is emerging quickly in the United States[48;49], clinical pharmacy in Switzerland is still very much focused upon patient-specific counseling on drug use.[265;266] With Swiss physicians increasingly dispensing drugs and the discipline of pharmacology also in the hands of physicians, comprehensive medication safety assessment potentially creates important professional opportunities for hospital pharmacists in Switzerland.

However, our survey showed that pharmacy staff resources, which are lower in Swiss hospitals than the European average, likely inhibit proactive efforts.[267] Consequently, targeted, effective and low-cost tools are required to address individual institutions' medication safety issues.

A carefully managed drug formulary is a cornerstone for safe medication use.[33] The American Society of Health-System Pharmacists recommends oversight by the pharmacy & therapeutics committee.[29;33]

Once drug products are approved for addition to an institution's formulary, regular medication use evaluations (MUEs) are warranted.[31-33;58] A systematic review of the current literature showed, that the trigger tool technology is the most efficient approach compared to incident report analysis, chart review and direct observation.[34] Establishing electronic means of data collection, management and exchange such as electronic prescribing, barcoding, automated dispensing and an electronic patient record not only improves medication safety[59;171;268-270], but also allows for more efficient collection and analysis of medication use related data[195;197].
Considering that different approaches to medication safety assessment reveal different types of medication errors, a combination of techniques is recommended. Specifically, the combination of trigger tool and incident report analysis is considered complimentary.[34]

Although spontaneous reporting does not provide an adequate denominator to allow for the calculation of true incidence rates, pharmacovigilance-derived data can reveal high severity medication use problems.[34]

As our survey showed, the use of incident reporting systems is common in Swiss hospitals.[267] Utilization of such systems already in place might be a time saving approach to systematic medication use evaluation. In addition, active promotion of incident reporting is associated with increased reporting, allowing for a more comprehensive view of an institution's medication use.

Sir Liam Donaldson, chair of the WHO's World Alliance for Patient Safety stated:

"The belief that one day it may be possible for the bad experience suffered by a patient (in one part of the world) to be a source of transmitted learning that benefits future patients (in many countries) is a powerful element of the vision behind the WHO World Alliance for Patient safety."

Hospital pharmacists in Switzerland can fulfill this belief by playing an important role in improving drug safety through a systematic, interdisciplinary approach at medication use evaluation.

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CURRICULUM VITAE

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	2008-2009	Medication Safety Fellowship, Dep. of Clinical Pharmacy, Medication Outcomes Center, University of California San Francisco, USA
	2002-2007	Postgraduate Education in Hospital Pharmacy FPH, Swiss Society of Public Health Administration and Hospital Pharmacists GSASA
	2005-2006	Certified First Responder, Emergency Paramedic School Zofingen, Switzerland
	2005	Certificate in Clinical Pharmacy, University of Tübingen in Collaboration with the London School of Pharmacy
	1996-2001	Diploma in Pharmacy issued by the Federal Department of Home Affairs, University of Basel, Switzerland
	1989-1996	Federal Matriculation Exam Type B, Gymnasium Alpenquai Lucerne, Switzerland
PROFESSIONAL EXPERIENCE	2010-present	Project Manger Drug Event Monitoring, Swiss Patient Safety Foundation, Zürich, Switzerland
	2011, March	Internship, Intermountain Healthcare, Salt Lake City, USA
	2010-2011	Council of Europe, EDQM, Pharmaceutical Care Group (Committee of Experts on Pharmaceutical Care, member of the Working Party and scientific collaborator), Strasbourg, France
	2008-2009	Junior Specialist, University of California San Francisco, Department of Clinical Pharmacy, Medication Outcomes Center, USA
	2007-2009	Head of Operations, Hospital Pharmacy, Hirslanden Clinic St. Anna, Lucerne, Switzerland
	2004-2007	Head of Clinical Pharmacy Unit, Bruderholz Hospital, Basel, Switzerland
	2003-2004	Head of Quality Assurance, Kantonsapotheke Zurich, Pharmacy of the University Hospital Zurich, Switzerland
	2001-2003	Hospital Pharmacist, part time 40%, Hospital Center Biel, Switzerland
	2002-2003	Product Manager Parenteral Nutrition, part time 60%, Fresenius Kabi Switzerland
	1999-2006	Deputy Pharmacist part time positions in various community pharmacies

TEACHING EXPERIENCE

2008	Clinical Nutrition, Pharmaceutical Sciences, University of Basel, Switzerland
2007	Pharmaceutical Production Techniques, University of Basel, Switzerland
2004-2007	Pharmacology for Nursing Staff, Nursing School BZG Basel-Stadt, Switzerland
2004	Annual Pharmacy Technician Training, GSASA
2004-2007	Pharmacy Technician Training, Bruderholz Hospital, Basel, Switzerland
2002-2004	Sales Agents and Nutritionists Training, Fresenius Kabi, Switzerland

INVITED TALKS

- 2011, Hospital Pharmacy Baden, Switzerland: Update on Medication Safety
- 2010, TEVA-Symposium on Medication Safety: "Ensuring the safety of drug administration", Bern, Switzerland
- 2010, GS1 Global Healthcare Conference, expert member of the "Panel discussion – the provider's view", Geneva, Switzerland
- 2009, Identification of drug-related problems in the hospital setting: a critical review of methods to assess medication safety, ESCP / GSASA Conference, Geneva, Switzerland
- 2004, Parenteral Nutrition – An Introduction, Training Nursing Staff ASI Ticino (in Italian), Switzerland
- 2004, On Being a Hospital Pharmacist, Pharmacy Workshop, University of Basel, Switzerland
- 2003, Seminar on Clinical Nutrition for Hospital Pharmacists, Hotel Continental, Lucerne, Switzerland
- 2003, GSASA Seminar on Parenteral Application, Hospital of Solothurn, Switzerland
- 2003, GSASA Seminar on New Drugs and New Dosage Forms, Hospital of Solothurn, Switzerland

PUBLICATIONS

- Meyer-Massetti C, Meier CR. Medication safety activities: The role of Swiss hospital pharmacists, EJHPP 2010, 16(6): 54-55.
- Meyer-Massetti C, Cheng CM et al. Medication safety assessment methods: how can institutions efficiently address drug-related problems? Am J Health-Syst Pharm. 2011; 68: 227-40.
- Frank O, Meyer-Massetti C et al. Quick Alert – Dosage errors with infusion pumps, 2010 email publication.
- Frank O, Meyer-Massetti C et al. Quick Alert – Sound alike / Look alike medications – Beware of confusions with a focus on IV products, GSASA-Journal - The Journal of the Swiss Society of Hospital Pharmacy. 2010 Jul.
- Frank O, Meyer-Massetti C et al. Quick Alert – The dangers of electrolyte infusions, 2010 email publication.
- Meyer-Massetti C. Cheng CM et al. The FDA Extended Warning for Intravenous Haloperidol and Torsades de Pointes: How Should Institutions Respond? J Hosp Med. 2010 Apr;5(4):E8-16.

- Cheng CM, Meyer-Massetti C, Kayser SR.
  A review of three stand-alone topical thrombins for surgical hemostasis, Clin Ther. 2009 Jan;31(1):32-41.
- 2007, “Step by Step” – Preventive measures and cleaning procedures to avoid contamination in the handling of cytotoxic drugs, 2008 Mepha Publication Special Edition.
- Swoboda S, Meyer-Massetti C, Hoppe-Tichy T. Interaction between an antiinfective agent and an immunosuppressant after liver transplantation, Med Monatsschr Pharm. 2006 May;29(5):179-82.

POSTERS

- 2010, The case of haloperidol: does the WHO pharmacovigilance database Vigibase offer comparative safety data?, Journées franco-suisses de pharmacie hospitalière, Sion, Switzerland (Junior Award “Best Poster”)
- 2010, Medication safety activities in Swiss hospitals: a status report on the role of the hospital pharmacist, Journées franco-suisses de pharmacie hospitalière, Sion, Switzerland
- 2009, Identification of drug-related problems in the hospital setting: a critical review of methods to assess medication safety, ESCP / GSASA Conference, Geneva, Switzerland
- 2009, Haloperidol and Torsades de Pointes: What is the evidence, ACCP Conference 2009, Orlando, USA
- 2006, Developing Guidelines for the Rational Use of Psychotropic Drugs on a Geriatric Ward, GSASA-Conference 2006, Biel, Switzerland
- 2006, Cleaning Validation of a Cleaning Device for Infusion Glass, GSASA-Conference 2006, Biel Switzerland
- 2001, Vitamins in Intravenous Lipid Emulsions – Benefit to the Premature Infant or to the Stability of the Emulsion, 30th European Symposium on Clinical Pharmacy, Antwerp, Belgium

SUPERVISED THESES

- 2011, Master’s thesis, Estelle Kaiser, Optimization of the medication use process in the homecare setting, University of Basel, Switzerland (Prof. Kurt Hersberger, Dep. of Pharmaceutical Care)
- 2011, Master’s thesis, Esther Locatelli, Drug event monitoring – development of drug safety indicators for the hospital setting, University of Basel, Switzerland (Prof. Dr. Christoph Meier, Dep. of Clinical Pharmacy)
- 2010, Master’s thesis, Simone Vaerini, Cardiac side effects of haloperidol – what is the evidence? University of Basel, Switzerland.
- 2007, Diploma Thesis, Patrizia Burger, Optimization of the Medication Safety Using Various Unit-Dose-Systems, University of Basel, Switzerland.
- 2006, Diploma Thesis, Ursula Penasa, Developing Guidelines for the Rational Use of Psychotropic Drugs on a Geriatric Ward, University of Basel, Switzerland.
- 2005, Diploma Thesis, Isabelle Brunner, Microbiological Monitoring in a Hospital Pharmacy, University of Basel, Switzerland.

OTHER ENGAGEMENTS

- 2011, Referee, American Journal of Health System Pharmacy

PROFESSIONAL ORGANIZATIONS

- ESCP, European Society of Clinical Pharmacy
- FIP, International Pharmaceutical Federation
- ACCP, American College of Clinical Pharmacy
- pharmaSuisse, Swiss Pharmacists' Association
- GSASA, Swiss Society of Public Health Administration and Hospital Pharmacists
- LAV, Pharmacists' Association of the canton of Lucerne