

International Experience: United States (and Canada)

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National Collaborative SCAR Initiatives

- No targeted, sustained (funded) US national initiatives analogous to those in other countries
- Institute for Safe Medication Practices (ISMP) periodically reviews severe ADRs reported to the FDA Adverse Event Reporting System
- Canadian Pharmacogenomics Network for Drug Safety includes SJS/TEN focus (pediatric; adults added later)
- NIH-funded organ-specific ADR networks (DILIN) subject to ongoing support for infrastructure
- Recognized need for infrastructure with perceived value to the hospital/institution for sustainability

January 16, 2014 — Special Report on Children

ADVERSE DRUG EVENTS IN CHILDREN UNDER AGE 18

Table 4. Drugs with reports of severe skin reactions

Drug	SJS/TEN*	All Cases**
Lamotrigine	66	335
Ibuprofen	32	242
Sulfamethoxazole; trimethoprim	16	70
Phenytoin	7	37
Carbamazepine	7	43
Amoxicillin	5	41

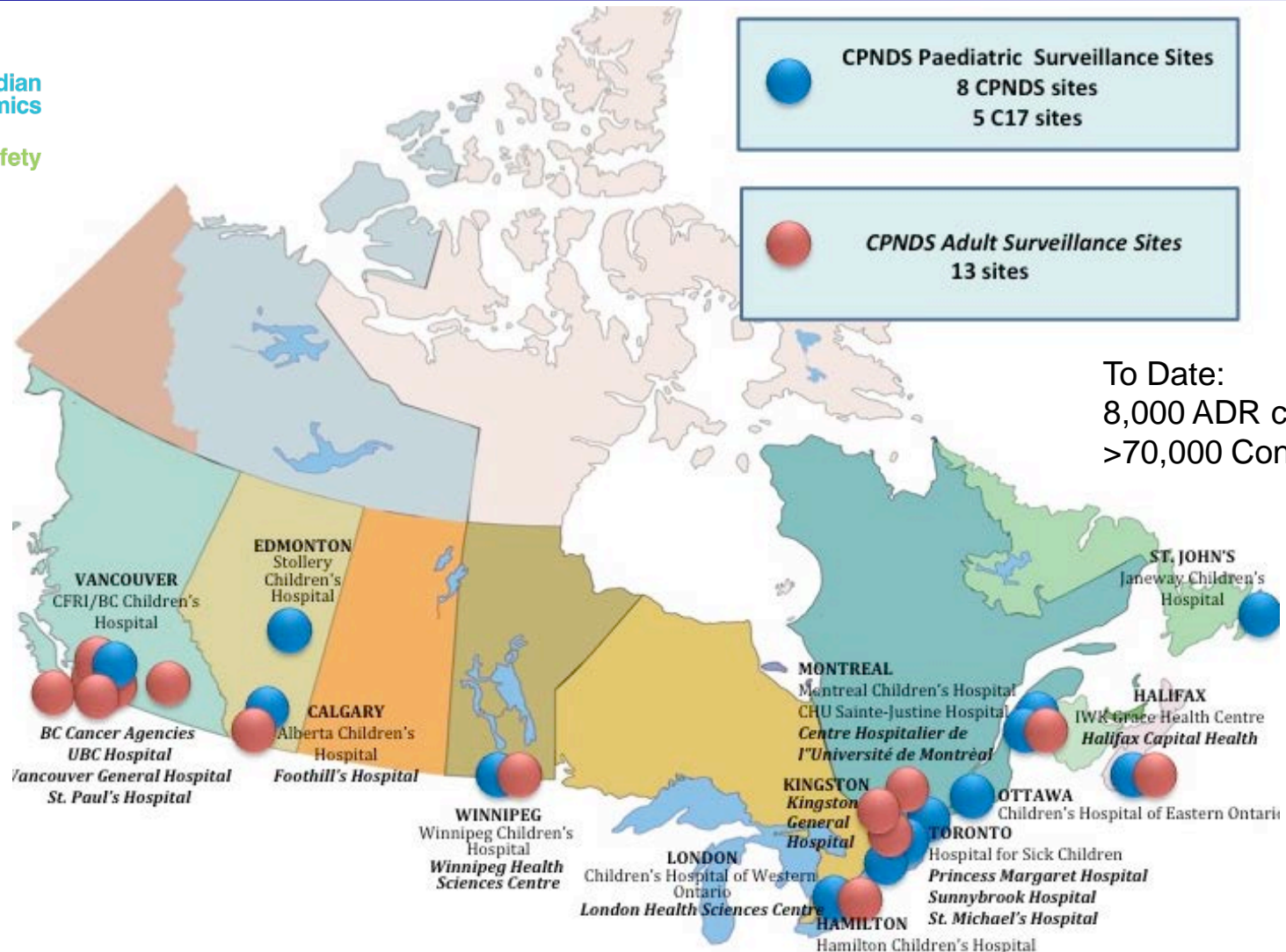
* Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

** Primary analysis group.

This is the second instance in which *QuarterWatch* has observed a disproportionate signal for lamotrigine and severe skin reactions. In the 2011 annual survey of patients of all ages, lamotrigine also led all other drugs in reports of severe cutaneous events. The FDA's required Boxed Warning notes that the rates of SJS/TEN appear to be higher in children than in adults, and less severe rashes may appear in 10% of treated patients. [17] Its first line use as adjunctive therapy for seizures should be reevaluated, and its approved use for maintenance in bipolar disorder reconsidered.

Reports of SJS/TEN associated with ibuprofen (MOTRIN, ADVIL) were instrumental in pushing the reported serious adverse event totals for ibuprofen (n=242) higher than other mostly over-the-counter (OTC) pain medications used in children, acetaminophen (TYLENOL, n = 137) and naproxen (ALEVE, n = 61). Also notable for ibuprofen were 34 cases of renal failure and impairment. Acetaminophen, on the other hand, had 32 reports of liver disorders, including 10 cases of liver failure, consistent with its known risks of liver damage.

Canadian Pharmacogenomics Network for Drug Safety: Bruce Carleton, PI



Canadian Pharmacogenomics Network for Drug Safety SJS/TEN

	SJS/TEN	HSS	Total Body Rash (to be defined)	Controls
Carbamazepine	10	13	7	143
Phenytoin	2	9	5	120
Lamotrigine	4	6	10	121
TOTAL	16	28	22	384

nature publishing group

ARTICLES

HLA-A*31:01 and HLA-B*15:02 as Genetic Markers for Carbamazepine Hypersensitivity in Children

CP&T 2013; 94: 142–149

U Amstutz¹⁻³, CJD Ross^{1,3,4}, LI Castro-Pastrana⁵, MJ Rieder⁶⁻⁸, NH Shear⁹, MR Hayden⁴, BC Carleton¹⁻³ and the CPNDS Consortium

CRITICAL REVIEW AND INVITED COMMENTARY

Epilepsia 2014; 55:496–506

Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions

*†‡§Ursula Amstutz, ¶Neil H. Shear, #Michael J. Rieder, **Soomi Hwang, ***†††Vincent Fung, §§Hidefumi Nakamura, †¶¶Mary B. Connolly, ###Shinya Ito, *†‡Bruce C. Carleton, and the CPNDS clinical recommendation group¹

Children's Mercy Kansas City Drug Safety Service

- ADR reporting required for JCAHO accreditation
- Reduce/eliminate harm within the hospital system
- Lead to development of pre-emptive interventions
- Feed research program: Pharmacogenomics of Pediatric Drug Safety (PPeDS)
- Led by a clinical pharmacology-trained pediatric Infectious Disease specialist
- Full-time dedicated clinical pharmacist
 - 803 unique ADR in 617 patients by >24 health care practitioners in 2014

Documentation of High Quality Phenotype Data in EHR

General Information

Suspected drug (original drug in profile, or new):

Select all that apply to this reaction

<input type="checkbox"/> Acetaminophen	<input type="checkbox"/> Cefprozil	<input type="checkbox"/> Fentanyl	<input type="checkbox"/> Nystatin	<input type="checkbox"/> Prochlorperazine
<input type="checkbox"/> Albuterol	<input type="checkbox"/> Ceftriaxone	<input type="checkbox"/> Ibuprofen	<input type="checkbox"/> Ondansetron	<input type="checkbox"/> Promethazine
<input type="checkbox"/> Amoxicillin	<input type="checkbox"/> Cephalexin	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Oseltamivir	<input type="checkbox"/> Ranitidine
<input type="checkbox"/> Amoxicillin/Clavulanate	<input type="checkbox"/> Cephalosporins	<input type="checkbox"/> Lorazepam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Risperidone
<input type="checkbox"/> Aripiprazole	<input type="checkbox"/> Chlorhexidine (CHG)	<input type="checkbox"/> Methotrexate	<input type="checkbox"/> Oxycodone	<input type="checkbox"/> Rituximab
<input type="checkbox"/> Aspirin	<input type="checkbox"/> Ciprofloxacin	<input type="checkbox"/> Metoclopramide	<input type="checkbox"/> Oxycodone/acetaminophen	<input type="checkbox"/> Sulfa drug
<input type="checkbox"/> Azithromycin	<input type="checkbox"/> Clindamycin	<input type="checkbox"/> Metronidazole	<input type="checkbox"/> Pegaspargase	<input type="checkbox"/> Sulfamethoxazole/Trimethoprim
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Codeine	<input type="checkbox"/> Midazolam	<input type="checkbox"/> Penicillin	<input type="checkbox"/> Valproic Acid
<input type="checkbox"/> Cefazolin	<input type="checkbox"/> Diphenhydramine	<input type="checkbox"/> Montelukast	<input type="checkbox"/> Pentobarbital	<input type="checkbox"/> Vancomycin
<input type="checkbox"/> Cefdinir	<input type="checkbox"/> Erythromycin	<input type="checkbox"/> Morphine	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Other:

Initial type:

Allergy/Hypersensitivity
 Side effect
 Unknown
 Religious/Preference
 Precaution
 Newly reported
 Not documented

Initial severity:

Unknown
 Life threatening: Severe
 Delay discharge: Severe
 Permanent disability: Severe
 Hospital admission: Severe
 Stop substance: Moderate
 Requires treatment: Moderate
 Change substance: Moderate
 Continue substance: Mild
 Newly reported
 Not documented

Final type:

Allergy/Hypersensitivity
 Side effect
 Unknown
 Religious/Preference
 Precaution
 Drug removed from profile

Final severity:

Unknown
 Life threatening: Severe
 Delay discharge: Severe
 Permanent disability: Severe
 Hospital admission: Severe
 Stop substance: Moderate
 Requires treatment: Moderate
 Change substance: Moderate
 Continue substance: Mild
 Drug removed from profile

If final type is religious/preference, precaution, or if a drug is removed from the profile, or the severity is MILD, there is no need to complete the remainder of this form.

Did this reaction occur in the past 30 days?

Yes No

Documentation of High Quality Phenotype Data in EHR

Cutaneous Symptoms - Cert, Baby sara

Refresh | Add | Print

Cutaneous Symptoms

Check all that apply

Cutaneous description:

<input type="checkbox"/> Angioedema	<input type="checkbox"/> Pustules
<input type="checkbox"/> Blisters	<input type="checkbox"/> Rash
<input type="checkbox"/> Bruising	<input type="checkbox"/> Red
<input type="checkbox"/> Fixed	<input type="checkbox"/> Red Man Syndrome
<input type="checkbox"/> Hives/wheals	<input type="checkbox"/> Round
<input type="checkbox"/> Irregular shape	<input type="checkbox"/> Scaling
<input type="checkbox"/> Itching	<input type="checkbox"/> Serum sickness
<input type="checkbox"/> Lip swelling	<input type="checkbox"/> Spreading
<input type="checkbox"/> Maculopapular	<input type="checkbox"/> Swelling
<input type="checkbox"/> Migratory	<input type="checkbox"/> Target lesion
<input type="checkbox"/> Pain	<input type="checkbox"/> Ulcerations
<input type="checkbox"/> Peeling	<input type="checkbox"/> Other:

Location:

<input type="checkbox"/> Head	<input type="checkbox"/> Palms of hands
<input type="checkbox"/> Face	<input type="checkbox"/> Extremity, left lower
<input type="checkbox"/> Eyes	<input type="checkbox"/> Extremity, right lower
<input type="checkbox"/> Mouth	<input type="checkbox"/> Soles of feet
<input type="checkbox"/> Neck	<input type="checkbox"/> All over
<input type="checkbox"/> Torso	<input type="checkbox"/> Head to toe
<input type="checkbox"/> Genitals	<input type="checkbox"/> Other:
<input type="checkbox"/> Buttocks	
<input type="checkbox"/> Extremity, left upper	
<input type="checkbox"/> Extremity, right upper	

Documentation of High Quality Phenotype Data in EHR

Medications

Within 2 weeks prior to the adverse reaction, was the patient receiving any of the following:

1. Any new over the counter substances?

Yes No Unknown

2. Any natural remedies?

Yes No Unknown

3. Any new foods?

Yes No Unknown

4. Any additional new medications?

Yes No Unknown

If able to name the medications, list all new medications that the patient may have received:

Documentation of High Quality Phenotype Data in EHR

Drug Safety Questionnaire - Cert, Baby sara

*Performed on: 08/15/2014 1032 CDT

General Informatic

Cutaneous Sympt

Noncutaneous Sy

Medications

Suspicious Drug #1

Suspicious Drug #2

Suspicious Drug #3

Management/Dur

Adverse Reaction

Suspicious Drug #1

<input type="radio"/> Acetaminophen	<input type="radio"/> Cefprozil	<input type="radio"/> Fentanyl	<input type="radio"/> Nystatin	<input type="radio"/> Prochlorperazine
<input type="radio"/> Albuterol	<input type="radio"/> Ceftriaxone	<input type="radio"/> Ibuprofen	<input type="radio"/> Ondansetron	<input type="radio"/> Promethazine
<input type="radio"/> Amoxicillin	<input type="radio"/> Cephalexin	<input type="radio"/> Lamotrigine	<input type="radio"/> Oseltamivir	<input type="radio"/> Ranitidine
<input type="radio"/> Amoxicillin/Clavulanate	<input type="radio"/> Cephalosporins	<input type="radio"/> Lorazepam	<input type="radio"/> Oxcarbazepine	<input type="radio"/> Risperidone
<input type="radio"/> Aripiprazole	<input type="radio"/> Chlorhexadine	<input type="radio"/> Methotrexate	<input type="radio"/> Oxycodone	<input type="radio"/> Rituximab
<input type="radio"/> Aspirin	<input type="radio"/> Ciprofloxacin	<input type="radio"/> Metoclopramide	<input type="radio"/> Oxycodone/acetaminophen	<input type="radio"/> Sulfa drug
<input type="radio"/> Azithromycin	<input type="radio"/> Clindamycin	<input type="radio"/> Metronidazole	<input type="radio"/> Pegaspargase	<input type="radio"/> Sulfamethoxazole/Trimethoprim
<input type="radio"/> Carbamazepine	<input type="radio"/> Codeine	<input type="radio"/> Midazolam	<input type="radio"/> Penicillin	<input type="radio"/> Valproic Acid
<input type="radio"/> Cefazolin	<input type="radio"/> Diphenhydramine	<input type="radio"/> Montelukast	<input type="radio"/> Pentobarbital	<input type="radio"/> Vancomycin
<input type="radio"/> Cefdinir	<input type="radio"/> Erythromycin	<input type="radio"/> Morphine	<input type="radio"/> Phenobarbital	<input type="radio"/> Other:

Duration of therapy: Less than 24 hours Greater than 24 hours Unknown

Previous therapy with this drug: Yes No Unknown

- Are there previous conclusive reports on this reaction? Yes (1) No (0) Unknown (0)
- Did the adverse event appear after the suspected drug was given? Yes (2) No (-1) Unknown (0)
- Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes (1) No (0) Unknown (0)
- Did the adverse reaction appear when the drug was readministered? Yes (2) No (-1) Unknown (0)
- Are there alternative causes that could have caused the reaction? Yes (-1) No (2) Unknown (0)
- Did the reaction reappear when a placebo was given? Yes (-1) No (1) Unknown (0)
- Was the drug detected in any body fluid in toxic concentrations? Yes (1) No (0) Unknown (0)
- Was the reaction MORE severe when the dose was increased, or LESS severe when the dose was decreased? Yes (1) No (0) Unknown (0)
- Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Yes (1) No (0) Unknown (0)
- Was the adverse event confirmed by any objective evidence? Yes (1) No (0) Unknown (0)

Naranjo Score:

Naranjo interpretation: Equal or > 9 = definite ADR 5 - 8 = probable ADR 1 - 4 = possible ADR 0 = doubtful ADR

Documentation of High Quality Phenotype Data in EHR

Drug Safety Questionnaire - Cert, Baby sara

✓ 📁 🚫 🖋️ 📅 ⬆️ ⬆️ 📄 📄

*Performed on: 08/15/2014 1032 CDT

Management/Assessment

How was the adverse reaction treated?

- Medication stopped
- Medication dose reduced
- Analgesic
- Antihistamine
- Epinephrine
- IV fluid
- Moisturizers
- Steroid (any formulation)
- Unknown
- Other:

Who provided treatment for the adverse reaction?

- PCP - Primary Care Provider
- ER
- Urgent Care
- Hospitalization
- Other:

***Plan:** [Right click for reference text](#)

- Family's questions and concerns were addressed
- Family was provided education regarding the assessment and given Adverse Reaction care card
- ADR notification entered for new reaction
- Suggested an IPT/Personalized Medicine or Allergy/Immunology consult to the team
- Other:

If completing more than one questionnaire for this patient, please answer this question only once

By performing this interview, did you discover any undocumented additional adverse reactions? Yes No

Documentation of High Quality Phenotype Data in EHR

D.	Substance	Category	Reactions	Severity	Type	C.	Est. Onset
✓	amoxicillin	Drug	Diarrhea	Continue Su...	Side Effect		

Type: Undesirable but expected response based on known properties (nausea, fatigue)

*Substance

 Free text

Reaction(s):



 Diarrhea

*Severity

At: [<not entered>](#)

Info source

Onset: [<not entered>](#)

Comments

11/05/2014 13:37 CST - IPT DSS: patient had diarrhea but completed course of therapy.

EHR Information Readily Accessible for Research Purposes: Cerner Discover e

Data Collection Event

[Exit Data Collection Event](#)

Walker Michael Hogshooter

Actions ▼

PPEDSCMH » Children's Mercy, Adel... » CMH_0001 » Data Collection Event

Expand All Collapse All

▼ **A. Case Triggers and Implicated Drugs**

Basic Information

✖

		Forms	Signoff Status	Lock Status	Combined Query Count
<input type="checkbox"/>		Basic Information	xN		0/0/0

Trigger and Drug

✖

		Forms	Signoff Status	Lock Status	Combined Query Count
<input type="checkbox"/>		Trigger and Drug	xN		0/0/0

▼ **B. Demographics (2 open, 0 responded, 0 closed)**

Demographics

✖

		Forms	Signoff Status	Lock Status	Combined Query Count
<input type="checkbox"/>		Demographics	xN		2/0/0

▼ **C. Medical History Information**

Medical History Information

✖

		Forms	Signoff Status	Lock Status	Combined Query Count
<input type="checkbox"/>		Medical History Information	xN		0/0/0


Sign-off Status:

- xN - Unsigned
- xY - Signed-off
- M - Modified
- E - No Data
- ⇅ - Final Signed-off

Lock Status:

- 🔒 - Locked
- ❄️ - Frozen
- 🔓 - Reopened

EHR Information Readily Accessible for Research Purposes: Cerner Discover e

Skin Reaction	
Show/Hide Annotation	
Skin Reaction length	
Date of skin reaction start:	dd-MMM-yyyy 19 - SEP - 2010 
Skin Reaction Clinical Symptom	
Generalized maculopapular rash	No
Facial Swelling/Angioedema	No
Erythema multiforme	No
Stevens Johnson Syndrome	No
Toxic epidermal necrolysis	No
Other	Yes
Unknown	No
Dermatology	
Evaluated by a dermatologist	Yes
If yes, was drug reaction suspected	Yes
Was a photograph taken?	No
Biopsy	
Biopsy conducted	No
Patch Test	
Patch test conducted	No

Developing ADR Infrastructure ...

- Currently no national initiative focused on SCAR in US
- Convince healthcare systems that ADR surveillance programs have value to the institution
- Standardize nomenclature and data collection processes
- Provides opportunity for research funds to be applied to the science, not infrastructure

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