

Implementation Guide

SSRI or SNRI – Thiazide Diuretics

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Under funding from AHRQ grants R21 HS023826 and R01 HS025984

MDIA publication No. 004

July 22, 2020

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Disclaimer of Conflict of Interest

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Funding Statement

This project was funded under contract/grant number XXXX from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the U.S. Department of Health and Human Services.

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Suggested Citation

Drug-Drug Interaction Clinical Decision Support. SSRI or SNRI – Thiazide Diuretics [Internet]. Available from: <https://ddi-cds.org/ssri-or-snri-thiazide-diuretics/>

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Introduction

Background

Ensuring that drug-drug interaction (DDIs) alerts are effective and meaningful is a longstanding clinical informatics issue, with alert fatigue serving as an issue that can negatively impact clinician response and patient safety. Existing alerting systems for DDIs are often simplistic in nature or do not take the specific patient and pharmacological contexts into consideration, leading to false or overly sensitive alerts.

Audience, Purpose, and Scope of this Implementation Guide

This document is designed to assist developers, clinicians, and pharmacists in applying this artifact toward enhancing clinical decision support (CDS) for potential drug-drug interactions between selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), and thiazide or thiazide-like diuretics.

Implementing and Using This Artifact

Description and Purpose of the artifact

This artifact aims to address risks of hyponatremia that arise with concurrent use of SSRI's or SNRI's alongside thiazide or thiazide-like diuretics. These three groups of drugs are widely known to affect sodium retention, with the resulting hyponatremia often requiring hospitalization. Sodium lab measurements, patient demographic information, and individualized patient history pertinent to hyponatremia risk are additionally taken into account through this artifact to assess hyponatremia risk for each patient. This artifact provides specific and contextualized alerts to enhance the ability of CDS systems to appropriately deliver pertinent information to the clinician.

Primary Use Case

(TODO)

Proposed Alerting Algorithm

The algorithm first identifies basic concomitant exposures of SSRI's or SNRI's and thiazide or thiazide-like diuretics. Among these concomitant exposures, if the patient has low sodium concentration (less than 130 mmol/L) within 7 days of the current order, a Class 1 (Red) alert is fired. If not, the algorithm assesses if demographic risk factors of either age (65 years old or older) or sex (female) are present. If so, a Class 2 (Orange) alert is fired. Otherwise, the algorithm then identifies if there are any ongoing drugs that the patient is taking that may cause hyponatremia, or if they have a history of any conditions associated with increased risk of hyponatremia. If any such risks are present, a Class 3 (Yellow) alert is fired.

Drug factors involved:

- SSRI's or SNRI's
- Thiazide or thiazide-like diuretics

Lab measurements involved:

- Sodium concentration

Patient demographic factors involved:

- Age
- Sex

Drugs known to cause hyponatremia:

- Amiodarone
- Angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB's)
- Antineoplastics
- Antiepileptics
- Haloperidols
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Risperidones
- Quetiapines

Conditions associated with hyponatremia risk:

- HIV or AIDS
- Adrenal insufficiency
- Heart failure
- Hepatic cirrhosis
- Malignancy
- Pneumonia

Guideline Interpretation and Clinical Decisions

Alert Classifications:

- Class 4: Green: No Special Precautions
 - Class 3: Yellow: Minimize Risk
 - For SSRI/SNRI – Thiazide rule:
 - Recommendation: Consider alternative. If combination is used, monitor serum sodium.
 - Rationale: Likely increased risk of bleeding
 - Class 2: Orange: Usually avoid
 - For SSRI/SNRI – Thiazide rule:
 - Recommendation: Consider alternative. If combination is used, monitor serum sodium.
 - Rationale: Increased risk of hyponatremia
 - Class 1: Red: Avoid Combination
 - For SSRI/SNRI – Thiazide rule:
-

-
- Recommendation: Avoid concurrent if possible. If combination is used, monitor serum sodium.
 - Rationale: Substantial risk of hyponatremia

Artifact Manifest

Table 1: Artifact Manifest

Filename	Purpose	Author(s)
SSRI-and-Thiazide-Graph-V6.pdf	The flow diagram of the decision tree for this algorithm	
ssri_snri_thiazide.drl	Computable Drools code to implement this algorithm's decision tree	
cql.zip	Computable CQL code for this algorithm.	
SSRI and SNRI value set	VSAC value set containing RxCUI's for SSRI and SNRI drugs.	
Thiazide and Thiazide-like diuretics value set	VSAC value set containing RxCUI's for thiazide and thiazide-like diuretic drugs	
Haloperidol value set	VSAC value set containing RxCUI's for haloperidol drugs	
Antineoplastic value set	VSAC value set containing RxCUI's for antineoplastic drugs	
Risperidone value set	VSAC value set containing RxCUI's for risperidone drugs	
Quetiapine value set	VSAC value set containing RxCUI's for quetiapine drugs	
Antiepileptic value set	VSAC value set containing RxCUI's for antiepileptic drugs	
Amiodarone value set	VSAC value set containing RxCUI's for amiodarone drugs	
Sodium concentration lab measurement value set	VSAC value set containing LOINC codes for sodium concentration lab measurements	
History of hepatic cirrhosis value sets: SNOMED , ICD10CM , ICD9CM	VSAC value set containing codes for hepatic cirrhosis conditions	
History of HIV / AIDS value sets: SNOMED , ICD10CM	VSAC value set containing codes for HIV / AIDS conditions	
History of heart failure value sets: SNOMED , ICD9CM	VSAC value set containing codes for heart failure conditions	
History of pneumonia value sets: SNOMED , ICD10CM , ICD9CM	VSAC value set containing codes for pneumonia conditions	
History of adrenal insufficiency value sets: SNOMED , ICD10CM , ICD9CM	VSAC value set containing codes for adrenal insufficiency conditions	
History of malignancy value sets: SNOMED , ICD10CM , ICD9CM	VSAC value set containing codes for malignancy conditions	
Discussion forum	Public discussion forum about the SSRI / SNRI – Thiazide rule.	

Artifact Relationship Diagram

Testing

Implementation Checklist

Boxwala et al.³ developed a multi-layered knowledge representation framework for structuring guideline recommendations as they are transformed into CDS artifacts. The framework defines four “layers” of representation:

1. **Narrative** text created by a guideline or CQM developer (e.g., the recommendation statement described as a sentence).
2. **Semi-structured** text that describes the recommendations for implementation as CDS, often created by clinical subject matter experts. It serves as a common understanding of the clinical intent as the artifact is translated in to a fully structured format by software engineers.
3. **Structured** code that is interpretable by a computer and includes data elements, value sets, and coded logic.
4. **Executable** code that is interpretable by a CDS system at a local level. This code will vary for each site.

This artifact is a **structured** representation of medical knowledge that contains code files that represent the source content (e.g., recommendation statement).

Figure 2: CDS Artifact Maturity Process



Prior to incorporating this artifact in a production setting, implementers should consider the following items:

- Analyze the purpose, clinical statement, and use case sections of this document to ensure that your organization understands and agrees with the intended goals of the clinical guideline on which this artifact is based.
 - Review the “clinical considerations” section of this document (including the decision log in Appendix B) to ensure that your organization understands and agrees with the decisions made during the process to convert the underlying clinical guideline to a structured, computable CDS artifact.
 - Technical staff should read through each of the files in the artifact manifest to understand their respective purposes and how they can be successfully incorporated into a clinical IT system. At the time of publication, many COTS EHR systems are unable to use CQL files natively and require a separate application to convert CQL code such that it can be used in those EHR systems. Implementers should work with vendors of their respective
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health IT products to understand their readiness to implement CQL code and any potential adverse impacts to existing functionality. In a pilot setting, developers have worked around existing EHR limitations by implementing a web service wrapper around a CQL execution engine. This is a non-trivial amount of work with two primary components:

- a CQL execution engine with a RESTful web service designed to accept requests for CQL execution and to respond with the calculated results, and
- modifications to the EHR system such that it will
 - trigger RESTful events to call the CQL execution engine,
 - interpret the response,
 - and reflect the CQL-generated recommendations and suggested actions in the EHR user interface.
- After incorporation into a development environment, the artifact should be exhaustively tested against predefined test cases. Additionally, testing should be conducted to ensure that implementation of the artifact has no adverse effect on the processing efficiency of the health IT system.
- Documentation and training materials for clinical staff should be drafted and distributed. These training materials should include descriptions of modified functionality, directions for interacting with CDS rules (if different than in the current system), and contact information for assistance in the event that functionality does not meet expectations.

Potential Reuse Scenarios

CQL code within this artifact was developed to enact a particular clinical guideline, but there are portions of the CQL code that are expected to be useful for other purposes.

- The `CDS_Connect_Commons_for_FHIRv102` and `FHIRHelpers` libraries included in the artifact define commonly used functions in CQL files and are not specific to the Statin Therapy for the Prevention and Treatment of Cardiovascular Disease (CVD) Electronic Clinical Quality Measure (eCQM) artifact. They are expected to be used with any other CQL file that could benefit from those functions.
- Selected code blocks from `Statin_Therapy_for_the_Prevention_and_Treatment_of_CVD_eCQM_Derived_FHIRv102` could be copied and reused in other CQL files. For example, some have expressed interest in the definition of pregnancy (based on the existence of either a condition code or observation code).

How Artifact Operates Within CQL

The Statin Therapy for the Prevention and Treatment of Cardiovascular Disease (CVD) Electronic Clinical Quality Measure (eCQM) artifact is composed of several files, but the primary focus of the artifact is the introduction of CQL files that can be used by any healthcare organization to properly identify populations of patients that require a specific message or clinical intervention. CQL is a data standard governed by Health Level 7 (HL7) that is currently

a Standard for Trial Use (STU). CQL expresses logic in a human-readable document that is also structured enough for electronic processing of a query. It can be used within both the CDS and CQM domains.

If you would like to learn more about CQL, there are a few resources (care of the [eCQI Resource Center](#)) that you should review:

1. [CQL STU Release 1 at HL7](#)
2. [CQL Tools on GitHub](#)
3. [CQL Formatting and Usage Wiki](#)
4. [CQL Online](#)
5. [CQL Q&As on the eCQI Resource Center](#)

How Artifact Operates Within Drools

A JBoss Drools rule engine (version 6.5.0.Final) uses a custom Java-based controller to load data from an OMOP database. A JDBC driver links the database to the rule engine. From the database, entities for each patients' relevant diagnoses, drugs, lab measurements, and other risk factors are identified and used in working memory. The rules written use this data to identify patients that satisfy criteria specified for each decision portrayed in the DDI decision tree. The rule engine iterates on a day-by-day basis throughout a specified study period and outputs alerts and relevant factors that occur on a specific day.

The Drools rule engine is available as a [GitHub project](#). This project includes a [Docker container](#) which can be used to virtualize the rule engine so that the audience can customize their own use case by choosing if they want to run one specific rule of interest, or if they have their own OMOP database connection that they wish to input to read data from.

After pulling the docker container using the command `docker pull ddicds/idia_rules`, The following command can be used to run the docker container over the default synthetic population:

```
docker run -v ~/simulated-run:/app/simulated-run -it --rm ddicds/idia_rules:localdb simulated
```

To run the rules over a custom database connection and/or specify a particular rule to isolate in the run, the following additional arguments can be added to the above command:

```
connectionURL={URL} ruleFolder={rule options listed below} schema={schema}  
user={user} password={password} sslmode=require
```

The `sslmode` argument is optional and its presence is dependent on the specific configuration of the database that the user wishes to connect to.

By default, all rules are run, but to specify individual rules, strings that can be passed into the `ruleFolder` argument include:

- `rules_acei_arb_ksparing_diuretics`
-

-
- rules_ceftriaxone_calcium
 - rules_citalopram_QT_agents
 - rules_clonidine_betablockers
 - rules_epi_betablockers
 - rules_fluconazole_opioids
 - rules_immunosuppressants_fluconazole
 - rules_k_ksparing_diuretics
 - rules_warfarin_antidepressants
 - rules_warfarin_nsaid
 - rules_warfarin_salicylates
-

Appendix A: Test Data

Table 2: Basic Tests

Patient ID	Age	Rule Branch	SSRI / SNRI	Thiazide	Low [Na ⁺] in last 7 days?	Patient female, or age 65 or older?	Drug-induced hyponatremia risk?	Conditions associated with hyponatremia risk?	RESULT: Recommendation	RESULT: Rationale
1574	58	GREEN: Basic concomitant with no additional risks	Sertraline 100 MG Oral Tablet	Hydrochlorothiazide 50 MG Oral Tablet	False	False	None	None	No special precautions	N/A
1575	58	RED: Patient has low sodium	Sertraline 100 MG Oral Tablet	Hydrochlorothiazide 50 MG Oral Tablet	True	False	None	None	Avoid concurrent if possible. If combination is used, monitor serum sodium.	Substantial risk of hyponatremia
1576	68	ORANGE: Patient is age 65 or older	Sertraline 100 MG Oral Tablet	Hydrochlorothiazide 50 MG Oral Tablet	False	True	None	None	Consider alternative. If combination is used, monitor serum sodium.	Increased risk of hyponatremia
1577	33	YELLOW: Patient has drug-induced hyponatremia risk	Sertraline 100 MG Oral Tablet	Hydrochlorothiazide 50 MG Oral Tablet	False	False	Phenytoin 50 MG Chewable Tablet	None	Consider alternative. If combination is used, monitor serum sodium.	Likely increased risk of hyponatremia

1578	28	YELLOW: Patient has condition associated with hyponatremia risk	Sertraline 100 MG Oral Tablet	Hydrochlor othiazide 50 MG Oral Tablet	False	False	None	Chronic diastolic heart failure	Consider alternative. If combination is used, monitor serum sodium.	Likely increased risk of hyponatremia
1579	28	GREEN: Basic concomitant with no additional risks	Sertraline 100 MG Oral Tablet	Hydrochlor othiazide 50 MG Oral Tablet	False	False	None	None	No special precautions	N/A

Appendix B: Decision Log

The decision log was generated per procedures published by Tso et al.,⁴ which incorporates and extends steps that Shiffman et al.⁵ outlined for translating clinical practice guidelines to CDS. Brief descriptions of the steps in this process are included in the following table:

Table 5: Definitions of Shiffman's Steps

Decision Category	Definition
Select Guidelines	Choosing specific guidelines and specific recommendations within the selected guidelines to be implemented
Markup	Identifying and tagging guideline knowledge components relevant to operationalization
Atomize	The process of extracting and refining single concepts from the narrative text into discrete decision variables
Deabstract	The process of adjusting the level of generality at which a decision variable or recommendation is defined to permit operationalization
Disambiguate	The process of establishing a single semantic interpretation for a recommendation
Build Executable Statements	Arranging the atomized, de-abstracted, and disambiguated decision variables and recommendations into executable statements that can be translated readily into computable statements
Verify Completeness	The process of making sure that each recommendation provides guidance in a situation that a clinician is likely to face
Add Explanation	A facility to describe the reasoning behind recommendations
Identify Origin	Identifying a source or origin in the clinical environment for each decision variable
Insert Recommendations	Identifying an insertion point in the care process for each recommended action
Define Action Type	Categorizing guideline-recommended activities per predefined action types
Define Associated Beneficial Services	Linking action types to associated beneficial services that offer design patterns for implementation in care
Design User Interface	Selecting and grouping user interface elements to best deliver CDS output

or who receive an order (prescription) for statin therapy at any point during the measurement period.

Decision Logs

Table 6: Decisions Based on "Atomized" Components of the Population Statements

Presence in Statement	"Atomized" Word or Phrase	Interpretation or Rationale

Several decisions were made outside the scope of the atomized words and phrases in the recommendation statements. These additional decisions were made based on the best available clinical knowledge and were encountered at various stages in the artifact development process.

Table 7: Additional Decisions

Decision Category	Concept	Rationale
Select guidelines		
Disambiguate		
Implementation guidance		
Deabstract		
Logic constraints to ensure clinical relevance:		
Add explanation		
Add explanation		
Deabstract		

Appendix C: Acronyms

ACA	Affordable Care Act
AHRQ	Agency for Healthcare Research and Quality
CAMH	CMS Alliance to Modernize Healthcare
CDS	Clinical Decision Support
CMS	Centers for Medicare & Medicaid Services
COTS	Commercial Off-the-Shelf
CQL	Clinical Quality Language
CQM	Clinical Quality Measurement
CVD	Cardiovascular Disease
eCQI	Electronic Clinical Quality Information
EHR	Electronic Health Record
FAR	Federal Acquisition Regulation
FFRDC	Federally Funded Research and Development Center
FHIR	Fast Healthcare Interoperability Resources
HDL	High-Density Lipoprotein
HHS	Department of Health and Human Services
HIT	Health Information Technology
HL7	Health Level 7
IT	Information Technology
LDL	Low-Density Lipoprotein
ONC	Office of the National Coordinator for Health Information Technology
PCOR	Patient-Centered Outcomes Research
PCORI	Patient-Centered Outcomes Research Institute
RSAs	Recommendations and Suggested Actions
USPSTF	U.S. Preventive Services Task Force

Reference List

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