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Research Report Template

Rhys Axon, Ph.D. Updated 20 November 2020

PROJECT TITLE & AUTHORS

Project Title:	*Temperature Effects on Chronic Lithium Toxicity in Arizona*	
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PROPOSAL CHECKLIST

Completed (Y)	Checklist item
Y	Project title is clear and concise.
Y	Names and emails for project advisor(s) and up to five students per group are provided.
Y	Abstract is no more than 250 words and retains headings

Y	Introduction provides a definition of the topic under study, importance of the topic, and the issue addressed by the study and is no more than one single-spaced page.
Y	There is NO literature review section
Y	Purpose of project is clearly and concisely stated
Y	Methods section uses headings and represents a summary of the methods used. (Actual methods used should be described if they were modified from the proposal.)
Y	Data analysis described is appropriate and responds to the purpose.
Y	Appropriate tables are included in the results section.
Y	Text of results section interprets the findings reported in the tables, not repeating them.
Y	The discussion section includes a description of the most important findings, and relates findings to the literature.
Y	The final section of the discussion is the limitations section.
Y	The conclusions respond to the purpose statement.

Y	Reference list is complete and contains appropriate references, and the reference style is applied correctly and consistently.
Y	Data collection/recording form(s) and/or questionnaire(s) are included in the appendix.
Y	Information is placed in the appropriate section—introduction, methods, results, etc.
Y	Template structure is maintained and all required sections are included. Red text instructions/examples are removed. Proposal is written in Times New Roman 12-point font and does not exceed 10 single-spaced pages (excluding appendices). Proposal has been spell-checked and grammar-checked.

ABSTRACT

Specific Aim: To examine the relationship between environmental temperature and the frequency of patients reporting chronic lithium toxicity to emergency departments in Arizona.

Methods: This study is a retrospective study that analyzed chronic lithium toxicity cases reported to the Arizona Poison and Drug Information Center (AZPDIC) via their database Toxsentry. The cases were screened for month and year of patient arrival, serum lithium levels, age, county, symptoms, outcome and pertinent lab markers such as sodium and serum creatinine levels upon arrival. Average ambient temperatures were collected corresponding to month, year, and county via the National Weather Service.

Main Results: Chart reviews allowed for 116 patient cases to be included in the analysis. Average age of patients was 51.5 (14.39) years. Average temperature of Arizona was 65.65°F where the collected temperatures were 67.8°F (15.51). The Chi-square test based on the month did not prove to be significant with $p=0.25$ for 95%. On the other hand, the ambient temperature was found to be statistically significant with $p<0.05$.

Conclusions: There is a correlation between increasing ambient temperatures and frequency of lithium toxicity; however, time of the year does not appear to be correlated with the frequency of Lithium toxicity.

INTRODUCTION

Lithium carbonate, or lithium citrate as the liquid formulation, are common mood stabilizing medications used for mental health disorders such as bipolar and as an adjunct agent in major depressive disorder. It has a very narrow therapeutic window of 0.6-1.2 mEq.[1] Lithium is renally eliminated and any disruption in filtration can cause lithium levels to rise and become toxic. Chronic lithium toxicity is defined as taking therapeutic doses of lithium and becoming symptomatic due to alteration in renal elimination causing elevated lithium levels requiring emergency medical treatment. Dehydration is a very common cause of acute kidney injury and can allow for the kidneys to retain lithium in the body, leading to toxicity. The common symptoms that require hospital visits are: nausea/vomiting, nystagmus, tremors, altered mental status, confusion, and seizure.[2] Chronic lithium toxicity does not include acute on chronic, therapeutic error, or acute ingestion of lithium. The study will be limited to hospital cases reported and consulted by the Arizona Poison Control Center in all Arizona counties excluding Maricopa.

Chronic Lithium toxicity cases are called to the Arizona Poison Control Center every year and occur in patients that have been taking them consistently for years. The toxicities are treated with fluids, supportive care and if the patient qualifies under the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) guidelines, dialysis. It is not easy to treat as there is no true antidote for chronic lithium toxicity. Lithium has been the gold standard of treatment for bipolar disorder for several years and unfortunately, it has a narrow therapeutic range as well as several drug interactions that can increase lithium levels.[2] Chronic poisoning is responsible for the highest risk of neurotoxicity.[1] If not treated at an emergency department in time, lithium toxicity can lead to Syndrome of Irreversible Lithium Effectuated Neurotoxicity (SILENT). Not much is known about this syndrome which can cause cerebellar dysfunction, dementia, or Parkinson's-like symptoms.[3] This is because Lithium needs time to distribute into the neural tissues and chronic toxicity results in a higher half-life when compared to acute overdoses.[2] One case report showed a 67-year-old male patient needing to go into a nursing home after 4 weeks in Intensive Care Unit due to chronic lithium toxicity. The patient was later diagnosed with SILENT due to neurological sequelae. This case report outlined how long hospital stays, high burden cost and poor patient outcomes are associated with chronic lithium toxicity.[4] Lithium is exclusively renally cleared and changes to hydration levels can play a large part in the development of chronic toxicity.[2] During the summer months, Arizona can reach upwards of 119°F (48.3°C) for those who are unprepared, this can lead to severe dehydration which in turn leads to Lithium toxicity.[3]

Previous studies have shown mixed results in the relationship between increased rates of toxicity and temperature. [6,7,8] These studies also were mainly focused on toxicity in an ambulatory care setting.[6,7,8] This study hopes to see if the relationship exists in Arizona, where the mean temperatures can vary from 50.1-101.1°F. The purpose of this study is to identify a correlation between seasonal temperatures and chronic lithium toxicity presentations in the emergency room department per Arizona Poison and Drug Information Center data.

METHODS

Study Design:

This will be a descriptive study that will use data obtained through a database, ToxSentry. This database is the database that the AZPDIC uses to record their cases of toxicities and exposures. The national weather service website will be used as well.[4] This study was approved by the University of Arizona Human Subjects Protection Program.

Subjects

The subjects included in this study were patients reported to the AZPDIC from the emergency department by the primary team asking for toxicology consultation in all counties of Arizona excluding Maricopa county. The patient needed to have a supratherapeutic lithium level (>1.2mEq/L), denied suicide ideation or overdose, and takes lithium chronically as a prescribed medication. Exclusion criteria includes patients ingesting any amount greater than prescribed (i.e. acute overdose), acute on chronic toxicity, lithium levels that were subtherapeutic, patients reporting therapeutic error, cases that remained at home, lack of zip code, and lack of date of patient presentation.

Measures

The majority of the data was collected from reports submitted by employees at the AZPIDIC to their database called ToxSentry. These reports come from inbound calls from hospitals asking for consultation on potential overdoses and are documented by the pharmacists including recommendations and consultations with toxicologists. The Average ambient temperature was collected using data publicly available through government funded weather reporting (weather.gov).[4]The data dictionary is shown in Appendix C2 The data extraction form for this study is shown in Appendix C3. The data dictionary shows the terms that were interpreted by the researchers when screening the profiles for inclusion into the study. The collection of the zipcode of the hospital and admission date were necessary to determine the ambient temperature that the patient was exposed to prior to their admission to the hospital. The age of the patients and Serum Lithium, sodium and serum creatinine levels were collected in order to provide baseline demographics of the patients collected as well as to ensure they were between the age range of 18-89. The relevant symptoms, treatment and outcome were collected to see if there was a difference in severity with patients in warmer ambient temperatures.

Data Collection

Data was collected through the ToxSentry database provided by the AZPDIC. The files were de-identified and only the necessary information was provided to the researchers. Ambient temperature was gathered from the government's publicly accessible data based on the county.

Data Analysis

Data analysis was done via Chi-square test on the frequency of cases by month as well as chi-squared test based on the ambient temperature of the month of admission. These values were then compared to the critical value in order to determine whether there was a correlation between the frequencies. The a priori p-value was set at 0.05.

Results

Demographic data is shown in table 1. Average temperature during the collected dates was 67.8 °F (15.51) with the range varying from 30-91.5°F. The average ambient temperature was similar to the reported average temperature of all of Arizona 65.5°F (p=0.069). It should also be noted that the average lithium level of patients was 2.25mEq/L which is about twice the amount of the therapeutic level. P-values could not be calculated for the demographics as this study is observational and there is no comparator group.

Out of 341 cases from 2017-2021, we included 116 patient cases based on our inclusion criteria and excluded 224 due to reports of overdose/suicide ideation, subtherapeutic levels, therapeutic error, lithium level was taken too early, and a patient staying home.

There was no significant correlation found based on the time of year and the frequency of lithium toxicity as shown in figure 2 (p=0.25), there does not appear to be a strong correlation seen in the sample; however, looking at the average ambient temperature in figure 3, there appears to be some correlation with frequency of lithium toxicity. Here the greatest number of cases were reported in the 80-90 Fahrenheit range and the p-value was found to be significant (p=0.000049).

Discussion

The primary finding of this study is that temperature and cases of chronic lithium toxicity reported to the AZPDIC do appear to be associated in regards to higher ambient temperature reporting higher cases. There does not appear to be an association between seasonal variation and cases of chronic lithium toxicity. Ambient temperature in all of Arizona is not uniform throughout the state, with higher (6,909 feet) and lower (141 feet) elevations posing a difficulty in reporting higher average temperatures. In the Italian study, they found an association between seasonal temperatures and lithium levels that was statistically significant. They found higher levels of lithium during the summer compared to spring and winter months (p=0.002).[8] There is a substantial summertime increase in temperature (up to 86–95 °C) in Italy, which correlates to our data average hotter temperatures. This study was a prospective study that looked at patients through 1989 to 1995. We find this observation to be closely related to our findings due to similar climate fluctuations and patient population undergoing similar temperatures that can cause perspiration and dehydration if not attended.

The Australian study conducted a similar study in Sydney, Australia looking at retrospective data of 2008-2018 serum lithium concentrations and compared it to the preceding 5 days maximum temperatures, month and season and did not find statistically significant differences between higher temperatures and higher lithium levels. The report expresses that Sydney, Australia does have a more temperate ambient temperature and narrower difference in change of temperature throughout the year, alongside the availability of access to air-conditioning which

can allow people to avoid harsh temperature changes.[5] We find this observation to be closely related to our seasonal temperature data finding due to most inhabitants of Arizona staying indoors during the summers and most homes containing air-conditioning. Under Arizona law, landlords must provide a rental unit with essential services, which includes air-conditioning under Arizona statute Title 33-1364(A). Correlating with the Australian study, a counterbalance of higher cases in the cooler months may be due to reduced hydration and viral illnesses compared to the warmer months which can skew the results into showing a lack of difference seasonally.

The study done in India did show that in subtropical countries, higher variability of lithium levels can be found when compared to different seasons, up to 25% variability with no significant change in maintenance dose. This was a retrospective study done on 101 patients in India, which followed their Lithium levels and compared the levels taken during the control month (October) to the more notable higher temperature months (June, July, and August). However, this is observational data, and it was not found to be clinically significant.[6] The authors do note an importance of frequent lithium level monitoring.

These findings indicate that inhabitants of Arizona counties, excluding Maricopa county, may not have the proper strategies to prevent dehydration lithium toxicity, such as via proper hydration, shade, and air-conditioning. Chronic lithium patients are followed by a physician for adequate level checks, which indicates providers may not be adapting their lithium dosages closely to prevent patients from coming into the emergency room for toxicity. Further exploration into lithium toxicity in the ambulatory setting at routine check ups is warranted to assess temperature and lithium level association in a warmer state such as Arizona. Primary care providers should be aware of dehydration risk for patients on lithium and hydration status should be assessed at each visit to prepare for severe heat warnings in the warmer months. This study shows that lithium dosages non toxic to patients in cooler temperatures may be toxic in warmer temperatures if hydration isn't addressed.

There were several limitations of this study. First, this was a retrospective study that used data from an outside consult service. Therefore, we can not properly assess if other causes such as drug-drug interaction or illness played a role in elevated lithium levels. The assumption was made that all patient charts were documented correctly by poison control staff. Controlled setting parameters would provide clearer answers on the association between temperature and chronic lithium levels. The results of this study should be generalized cautiously to patients that arrive at an emergency department with chronic lithium toxicity in other states.

Conclusion

The ambient temperature of the environment appears to have some correlation with the frequency of Lithium toxicity. However, there does not appear to be a correlation between the time of the year and the frequency of Lithium toxicity. This may be due to the variability in the temperatures of Arizona.This might indicate that higher temperatures may lead to increases of Lithium concentrations of patients either due to dehydration or some other variables. Further research needs to be done in order to prove this correlation as there are several confounding variables that could also be affecting this data due to the observational nature of the study.

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TABLES AND FIGURES

Table 1.

Characteristics of Study Subjects

Average Temperature (F)	67.9 °F	(15.51)
Age (Mean, SD)	51.1 yr	(14.40)
Serum Li level	2.25 mEq/L	(0.78)
Na	136 mEq/L	(4.23)
Scr	1.4mg/dL	(0.94)
County (N, %)		
	Cochise	(3, 2.59%)
	Coconino	(9, 7.76%)
	Mohave	(10, 8.62%)
	Navajo	(4, 3.45%)
	Pima	(77, 66.37%)
	Pinal	(2, 1.72%)
	Yavapai	(8, 6.90%)
	Yuma	(3, 2.58%)
Symptoms (%)		
	Altered Mental Status	(63.25%)
	Tremor	(30.77%)
	Dizziness	(17.09%)
	Gastrointestinal effects such as	

Nausea/Vomiting/Diarrhea (22.22%)

Outcome (N, %)

Patient was discharged (78, 67.24%)

AZPDIC signed off, normal Li levels (29 , 25%)

Unknown status (8, 6.90 %)

Death (1, 0.86%)

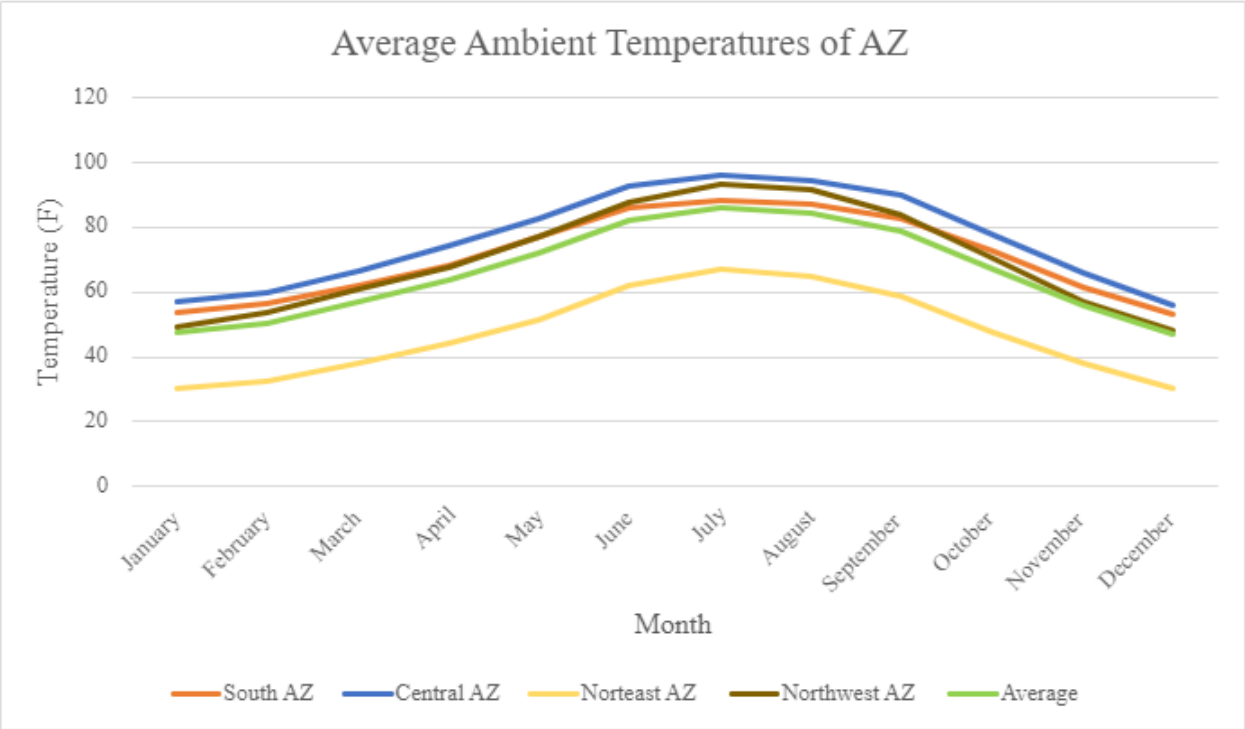

Fig.1 Average Ambient Temperatures in Arizona from 2000-2021 using data provided by Weather.gov.[4]

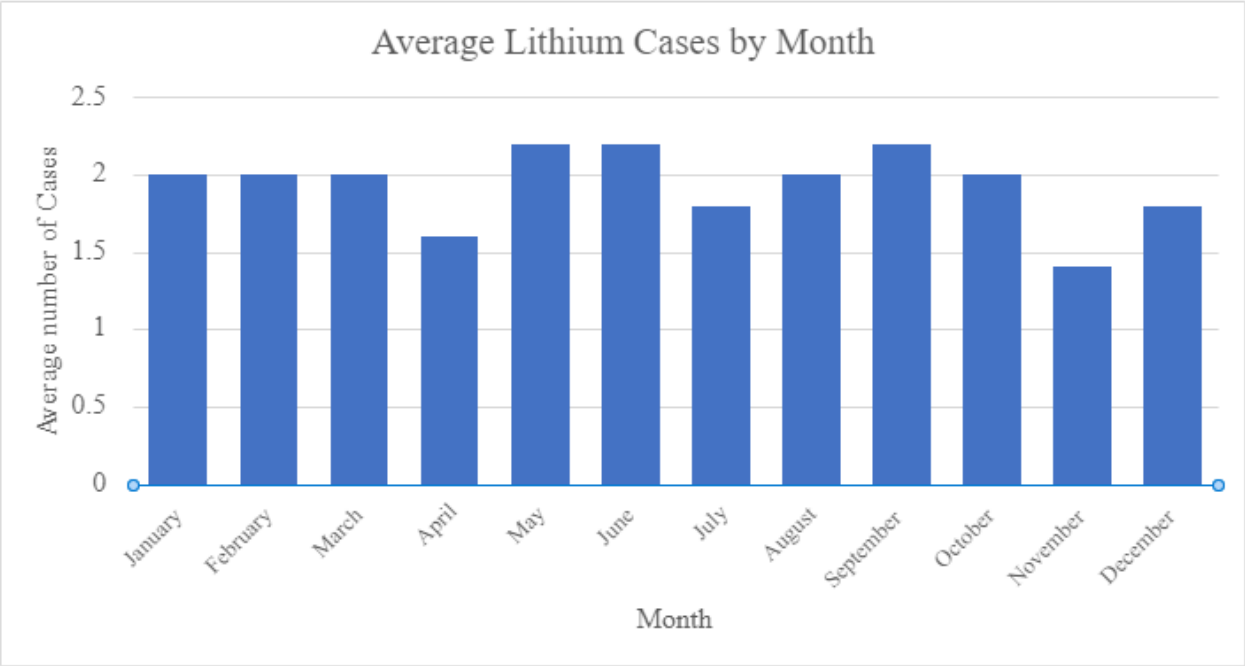

Fig.2 Average Lithium Cases by month. Data taken from ToxSentry cases January 1, 2017-December 31, 2021

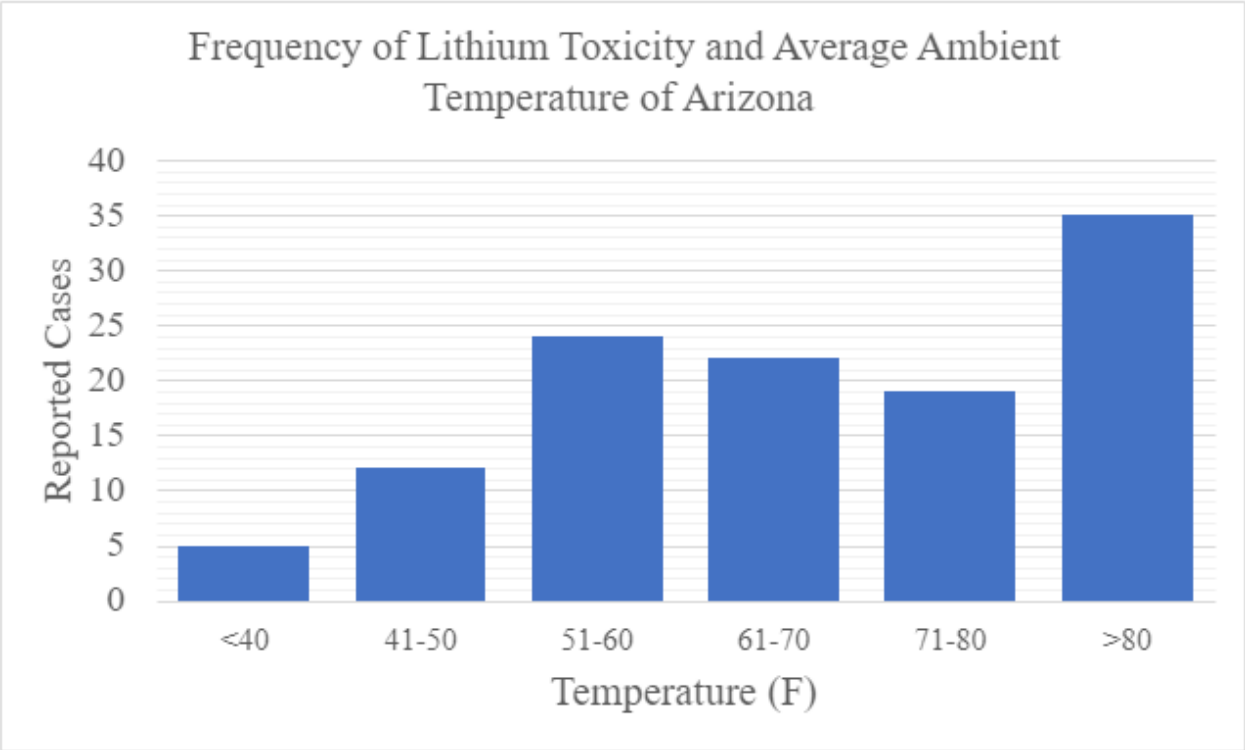

Fig. 3 Frequency of Lithium Toxicity compared to the ambient temperature of Arizona at the month of admission. Using data from Toxsentry and weather.gov from January 1, 2017-December 31, 2021

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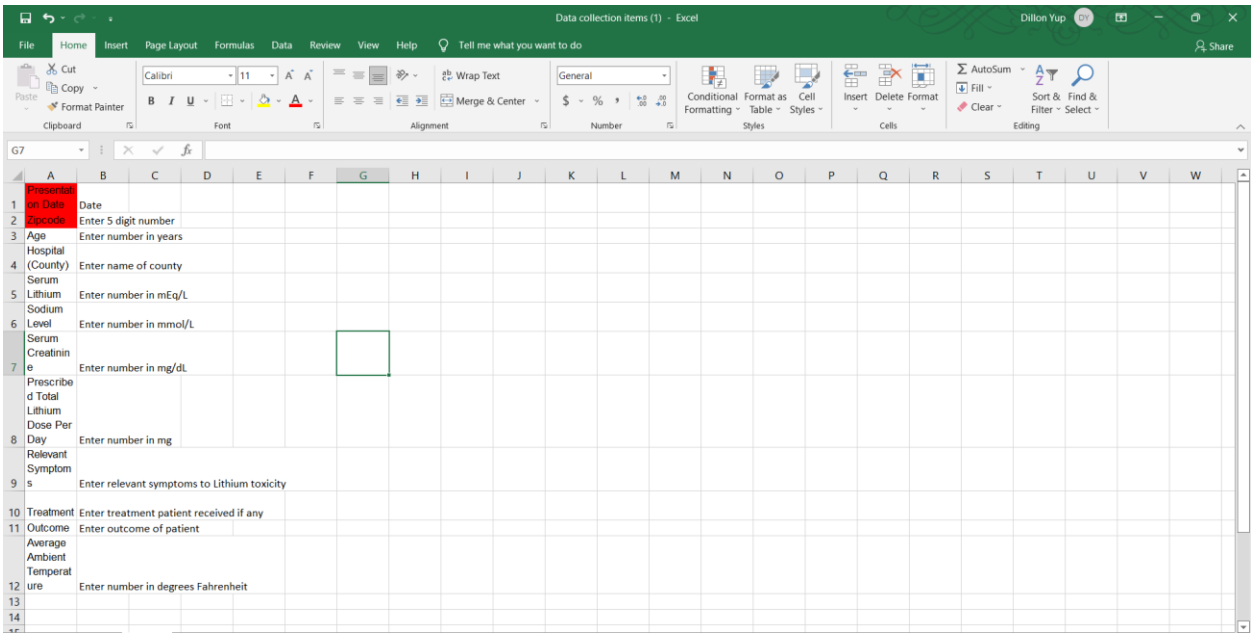
APPENDICES

Appendix A1: Data Dictionary



	A	B
1	Presentation Date	Date
2	Zipcode	Enter 5 digit number
3	Age	Enter number in years
4	Hospital (County)	Enter name of county
5	Serum Lithium	Enter number in mEq/L
6	Sodium Level	Enter number in mmol/L
7	Serum Creatinine	Enter number in mg/dL
8	Prescribed Total Lithium Dose Per Day	Enter number in mg
9	Relevant Symptoms	Enter relevant symptoms to Lithium toxicity
10	Treatment	Enter treatment patient received if any
11	Outcome	Enter outcome of patient
12	Average Ambient Temperature	Enter number in degrees Fahrenheit
13		
14		

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APPENDIX A2: Data Entry Sheet