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Polypharmacy and Use of Psychotherapeutic Agents Leading to Falls in Patients with Dementia: Proof of Relationship

Ethan Schonfeld*[1], Andrew Becker, MS[2], Katrina Tate, MS[2], Meghana Moodabagil, MS[2]

Ricardo G. Senno, MD, MS, FAAPMR[2]

[1]Stanford University, Stanford, CA

[2]Chicago Medical School, Rosalind Franklin University, Chicago, IL, USA.

ethanschonfeld@gmail.com

***Corresponding Author:** Ethan Schonfeld, Stanford University, Stanford, CA, USA.*

Abstract

Objective: *To analyze the ramifications of polypharmacy and the prescription of psychotherapeutic agents among participants having dementia.*

Design: *IRB approved, 3 month observational study.*

Setting: *3 memory care assisted living communities in Illinois.*

Participants: *Mild/moderate/severe dementia residents (N=153). 51 males and 102 females. 65 to 99 years old.*

Interventions: *All participants were administered the Mini Mental State Examination (MMSE) one time to determine the level of their dementia.*

Main Outcome Measures: *Level of dementia was assessed through the MMSE. Past medical history (Parkinson's disease, type of medications, number of medications, etc…) was gathered from the medical chart. Social history (tobacco use, hearing loss, etc…) was obtained through power of attorney questionnaire.*

Results: *A p-value of 0.0727 was obtained from a Pearson's Chi Squared Test of Independence for Number of Medications and Number of Falls. A p-value of 0.0385 was obtained from a Chi Squared Test of Independence for Use of Psychotherapeutic Agents and Number of Falls.*

Conclusions: *Participants taking excess amounts of medications, termed polypharmacy, may be at a greater risk of experiencing falls. Furthermore, those participants using psychotherapeutic agents seem to be at a particularly greater risk to fall.*

Keywords: *Dementia; Psychotherapeutic Agents; Falls; Polypharmacy; Poly-physician; Memory Care Community.*

Introduction

Older aged residents living at assisted memory care communities suffer from dementias - chronic progressive conditions involving issues with cognizance, balance, memory, motor control, proprioception, and a decreased quality of life[1]. After the diagnosis of dementia, patients' conditions can worsen for several reasons; a high number of falls is one of these. Falls can have subsequent complications such as traumatic brain injury (concussions), hip fractures and skin lacerations, all of which can worsen dementia.

Another tentative explanation for the worsening of dementia is polypharmacy, the prescription of either too many medications or the prescription of incorrect medications. Psychotherapeutic agents are the most commonly misused drugs by physicians in the older aged population suffering from dementia[2]. For the purpose of this study, polypharmacy, based

off of the definition in the Bushardt et al study titled: "Polypharmacy: Misleading, but manageable", is determined to be the prescription of six or more medications to an older age adult[3] or as stated, the prescription of incorrect medications. In the Montamat et al study titled "Overcoming problems with polypharmacy and drug misuse in the elderly", polypharmacy is "associated with factors such as the number and severity of illnesses, hospitalization, number of physicians seen, number of pharmacies used, and possibly increased patient age"[2]. The hospitalization and increased patient age described in Montamat's research are indicative of falling in dementia patients. Our study illustrates the present link between polypharmacy and falls.

Methods

The methods for this observational study involve a design similar to a previous study by Schonfeld et al titled: "Correlation of Hearing Loss and Chronic Falling Among Patients with Dementia in Three Memory Care Communities"[4] which was published in the Annals of Long Term Care. The studies differ in their data analysis. This current study seeks to offer an alternate explanation as to which factors contribute to older aged adults with dementia falling.

Summarizing the methods from Schonfeld et al: "The study took place in 3 freestanding assisted-living memory-care facilities in Illinois. A total of 153 residents with dementia were studied, 51 of whom were men and 102 of whom were women. Participants' ages ranged from 65 to 99 years. This was an institutional review board (IRB) approved study, and, given the loss of decision-making capacity among the participants, consent was obtained from the power of attorney (POA) agent. Data was collected from March 1, 2016 through July 31, 2016. Each participant was studied for a total of 90 continuous days within this 4-month study period; the mini-mental state examination (MMSE)[5] was administered at the end of an individual's 90-day period. The MMSE was administered in a private room; participants and their POA agent had the option to stop, postpone, or split the MMSE into multiple sessions. The MMSE was administered to participants at all facilities during the study period between 9am and 12 noon to avoid changes in behavior related to sundowning, which refers to the change in cognition that can occur later in the day in some persons with dementia[6]. Of the 153 participants enrolled, 51 residents were from site A, 68 from site B, and 34 from site C. The number of each participants' falls in the 3 months prior to the administration of the MMSE was recorded. Age, gender, and medical history (eg, Parkinson disease [PD], osteoporosis, hyperlipidemia, hypothyroidism, chronic obstructive pulmonary disease [COPD], hypertension, other chronic diseases) were gathered from each participants' medical record. Additionally, the number of medications taken by each participant and their use of antibiotics also were analyzed. Because of participants' dementia and associated decreased cognition, the social history was obtained through a questionnaire and conversation with each participants' POA agent. The social history characteristics considered were tobacco use, military service, prior participation in athletics, and current use of glasses and/or hearing aids. De-identified, encrypted data was compiled on an Excel Spreadsheet and strict IRB guidelines were followed."[4]

Differing from the previous research, this study focuses on the relationship between *Number of Falls* and *Number of Medications* (Test 1). A Pearson's Chi Squared Test[7] of Independence was computed for the studied relationship. A Chi Squared test was also run to determine whether a relationship exists between *Number of Falls* and *Use of Psychotherapeutic Agents* (Test 2). In this study we did not differentiate on drug class.

The Chi Squared Test of Independence sets two hypothesis: a null and an alternative. The hypothesis for Test 1 are as follows:

(Null) H_{01} = There is no relationship between the *Number of Falls* and the *Number of Medications* for a dementia patient in an assisted living community. The two variables are independent.

(Alternative) H_{a1} = There is a relationship between the *Number of Falls* and the *Number of Medications* for a dementia patient in an assisted living community. The two variables are not independent.

The Chi squared test assumes the null hypothesis (H_0) and calculates the probability of getting a result (formulated as the Chi Squared Statistic, X^2) as correlated or having greater correlation than what is in the observed data (Table 1). The test requires comparison of two categorical variables.

For the Chi Squared test, the data for *Number of Falls* was split into two groups as follows:

<2 Falls (N_1=100)

≥2 Falls (N_2=53)

The value of 2 falls was chosen to split the data. Splitting the data at 2 falls gives one group 53 participants and the other 100 participants. Because number of falls is an integer value, this was the optimal cut off to maintain equally sized groups. More importantly, two falls in three months is a good indicator of the type of faller a participant is. Those who fall less than two times in three months likely fall from a obvious circumstance such as tripping over a wheelchair. However, those falling two or more times most likely have a complex explanation for the falls. This examination of the type of fall experienced in a nursing home is crucial to understanding how to prevent these falls[8]; by splitting the data by the 2 fall statistic, an emphasis is placed on complex fall triggers.

Additionally, the other categorical variable *Number of Medications* was split into three groups:

Typical: [0 to 6] medications

High: [7 to 10] medications

Severe: [11 or more) medications

The cutoff of 6 medications to differentiate between typical and high fits this study's definition of polypharmacy (greater than the prescription of six medications). Therefore, all "high" or "severe" medicated participants by this definition have polypharmacy. To differentiate between "high" and "severe" medicated participants, the value of eleven medications was determined to be the cutoff. Based on the work of Viktil et al in the study "Polypharmacy as commonly defined as an indicator of limited value in the assessment of drug-related problems", eleven drugs is a good estimate of extreme polypharmacy[9].

The hypothesis for Test 2, examining psychotherapeutic agents, are as follows:

(Null) H_{02} = There is no relationship between the *Number of Falls* and the *Use of Psychotherapeutic Agents* for a dementia patient in an assisted living community. The two variables are independent.

(Alternative) H_{a2} = There is a relationship between the *Number of Falls* and the *Use of Psychotherapeutic Agents* for a dementia patient in an assisted living community. The two variables are not independent.

The prescription of psychotherapeutic agents was gathered from the participants' medical chart. In the Chi Squared Test, participants were considered as being prescribed the medication or not having the medication prescribed. 71 participants had a prescribed psychotherapeutic agent(s); 82 participants had no prescribed psychotherapeutic agent(s).

For Test 2, falls were split into the following categories:

During the studied three month period:

Obvious: 0 or 1 fall

Regular: 2, 3, or 4 falls

Chronic: 5 or more falls

The first interval of 0 or 1 fall was chosen to account for obvious falling, as described in Test 1.

The second interval ends at 4 because in previous research the value of 5 falls in a three month period was categorized to be the cutoff for "chronic falling"[4]. It is important to differentiate between (no falls / one random fall), (regular falling), and (chronic falling), in order to best consider the effects of psychotherapeutic agents on falling.

Results

The contingency table (see Table 1) shows the raw data for the *Number of Medications* vs. *Number of Falls*. The expected values table (see Table 2) shows the theoretical values, assuming no correlation, used to calculate the Chi Squared Statistic (X^2) for the *Number of Medications* vs. *Number of Falls* (Test 1).

Table1. *Contingency Table Test 1 (Observed Values)*

	Typical Medication [0-6]	High Medication [7-10]	Severe Medication [≥11]	Total
<2 Falls	17	46	37	100 (N1)
≥2 Falls	9	15	29	53 (N2)
Total	26	61	66	153 (N)

Table2. *Expected Values for Chi Squared Test 1*

X^2	Typical Medication [0-6]	High Medication [7-10]	Severe Medication [≥11]
<2 Falls	≈16.99	≈39.87	≈43.14
≥2 Falls	≈9.007	≈21.13	≈22.86

To perform the Chi Squared for Test 1, certain conditions must be met, these are addressed below:

- Study participants, as defined by IRB, were composed of a sample from a population of over 1530 residents.
- *Number of Medications* and *Number of Falls* are both categorical variables.
- Expected Values are all greater than 5 (see Table 2).

Let α = 0.10

This value (α) of 0.10 is the significance level for Test 1. A finding of (p-value) underneath this threshold would imply that we may reject that there is no relationship between the *Number of Falls* and the *Use of Psychotherapeutic Agents* for a dementia patient in an assisted living community (null hypothesis H_{01}) and conclude the alternate hypothesis H_{a1}, that there is a relationship between the variables.

Degrees of Freedom = (# of rows -1) X (# of columns -1)

(Test 1) = (2-1) X (3-1) = 2

The rows and columns refer to the observed values table (see Table 1).

To calculate X^2 statistic[10]:

$$\chi^2 = \Sigma \frac{(Oi-Ei)X(Oi-Ei)}{Ei} \approx 5.242098$$

Where O_i is the i_{th} observed value and E_i is the i_{th} expected value.

Therefore: p-value ≈ 0.0727

0.0727 < (α = 0.10), therefore we reject H_{01} and have statistical evidence to suggest that a relationship exists between *Number of Medications* and *Number of Falls*. We prove that these two variables are not independent.

For further examination of the relationship between *Number of Medications* and *Number of Falls,* a line graph is later used. (See Figure 1).

The contingency table and expected counts table used to calculate the Chi Squared Statistic (X^2) for the *Number of Falls* and the *Use of Psychotherapeutic Agents* is shown (see table 3,4) (Test 2):

Table3. *Contingency Table Test 2 (Observed Values)*

	0 or 1 Fall (Obvious Falling)	2,3, or 4 Falls (Regular Falling)	5 or more (Chronic Falling)	Total
Use of Psychotherapeutic Agents	41	18	12	71
No Use of Psychotherapeutic Agents	59	19	4	82
Total	100	37	16	153

Table4. *Expected Values for Chi Squared Test 2*

X^2	Typical Medication [0-6]	High Medication [7-10]	Severe Medication [≥11]
Use of Psychotherapeutic Agents	≈46.41	≈17.17	≈7.42
No Use of Psychotherapeutic Agents	≈53.59	≈19.83	≈8.58

Conditions to perform Chi Squared test of Independence:

- Study participants, as defined by IRB, were composed of a sample from a population of over 1530 residents.
- *Number of Falls* and *Use of Psychotherapeutic Agents* are both categorical variables
- Expected Values are all greater than 5 (see Table 4).

Let α = 0.10

Degrees of Freedom (Test 2) = 2

To calculate X^2 statistic:

$$\chi^2 = \Sigma \frac{(Oi-Ei)X(Oi-Ei)}{Ei} \approx 6.5098$$

Therefore: p-value ≈ 0.0385

0.0385 < (α = 0.10), therefore we reject H_{02} and have statistical evidence to suggest that a relationship exists between *Number of Falls* and the *Use of Psychotherapeutic Agents*. We prove that the two variables are not independent.

Figure 1 (below) explores the relationship between *Number of Medications* and *Number of Falls* in more detail.

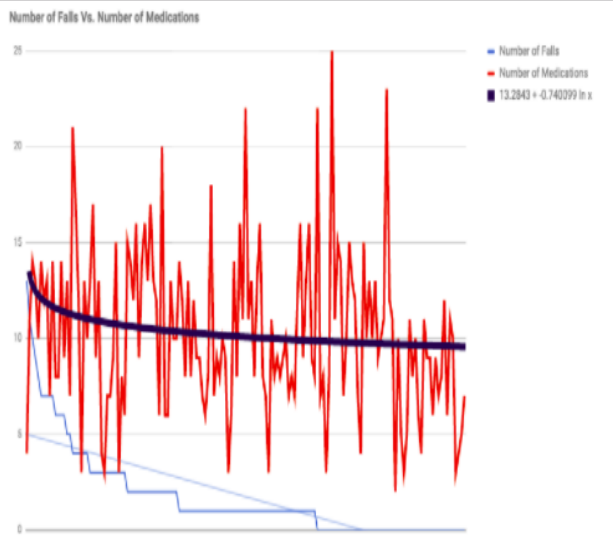

Figure1. *Number of Medications Vs. Number of Falls*

Figure 1 shows an increasing relationship between the *Number of Medications* given and the *Number of Falls* through a regression analysis.

The x-axis represents individual subjects with some subjects embedded within peaks and valleys.

The y-axis represents both the number of falls and the number of medications. This should be thought of as two graphs superimposed on each other.

The thick blue line is the regression of number of medications. Notice that it is logarithmically decreasing.

The number of falls is shown with the stepped blue line with its superimposed regression. As the graph moves from left to right, the number of falls decreases. With respect to the number of falls, the number of medications is shown with the red line.

For example, at x=0: this participant fell 13 times with a number of medications equal to 4. Similarly, for the value to the immediate right of it, marking a participant who fell 10 times, the number of medications is equal to 14. The line appearing in black is the logarithmic regression of the number of medications. The equation for the regression is f(x)=13.2843-0.740099 ln(x).

The regression line, which is a best fit for the data, is increasing from right to left. Therefore it is predicted that as the number of medications increases, so too then does the number of falls. Simultaneously, it can be stated that as the number of medications decreases, so too then does the number of falls (reading the graph from left to right). Those participants falling more had on average, a greater amount of medications. These results seem to support the hypothesis that polypharmacy accounts for an increased number of falls.

However, there is a subset of the studied population that experienced chronic falling (5 or more falls) and yet had a typical number of medications (0-6). An example of this is 4 medications for the participant who fell 13 times. A possible explanation for these outliers is the inappropriate use of psychotherapeutic agents, which can lead to increased falling. This warrants further study to analyze this subset.

Discussion

The number of medications was obtained from the resident's medical chart. However, as all the study's participants were diagnosed with dementia, it is likely that only some of the prescribed medications are being taken (compliance bias). This is especially important because discrepancies in usage of medication is most correlated to old age and polypharmacy[11]: both two prevailing elements of this research population. Thus

the actual effect of polypharmacy on falling may be greater than the observed relationship. Therefore, it is likely that while the study showcases a relationship between *Number of Falls* and *Number of Medications*, the theoretical impact of medications on falls in all likelihood is greater than what this study is able to show and the study's results should therefore be considered all the more relevant.

Symptoms of polypharmacy have been previously noted by physicians working with older aged patients. The effects were described by Dr. Stephen Sinatra as, "In addition to cardiovascular issues, these patients often had profound weakness and lethargy, disorientation, sleeplessness, nightmares, depression, heart failure symptoms (even when they didn't have heart failure), constipation, and episodes of falling… With age the body becomes less able to handle multiple medications and drugs are more likely to cause adverse reactions"[12]. A danger of polypharmacy is that many medications have effects that negate each other -- leaving the patient with only the adverse and side effects of each of these drugs[13].

We also suggest that a potential explanation for a chronic number of falls is the presence of multiple physicians working for a certain patient, we can call this situation "poly-physician". Participants with dementia often have a primary-care doctor and specialists. This repeatedly leads to each physician prescribing medications without coordinating with other doctors and can exacerbate polypharmacy[14]. In our study, the resident, when admitted to the memory care facility, was assigned to yet another physician. The intent is for this physician to coordinate care under one doctor; however, the Power of Attorney often chooses to continue care with all previous clinicians. With an increase in the number of physicians, it is probable that the number of medications is grossly increased.

Another factor relating to the increase of medications arises in a detailed look at the relationship between falls and medication. Once a participant falls, it is often procedure for them to be admitted into the emergency department at a local hospital[15,16]. Here it is likely that more medications are added; furthermore, the clinician can add medications to address new conditions arising from the fall such as major injuries, fractures, or skin lacerations -- conditions that can call for the use of pain medications[17]. These increased medications in turn can contribute towards more falls, thereby sending the resident back to the emergency department and continuing a cyclical process.

The authors suggest a drastic change in the way medications are prescribed to older aged patients -- especially those at a high fall risk such as the study's participants with dementia. Medication needs to be more carefully prescribed and physicians must seek to limit the total number. This can be accomplished through the use of pharmacogenomic testing[18]. Pharmacogenomic testing is an innovative method that can be used to pinpoint which medications will work for a specific patient. By doing so physicians may seek to limit overprescription and only prescribe drugs that have a genetic fit and are likely to function effectively.

To limit the number of falls for an older aged resident, doctors should seek to limit the prescription of psychotherapeutic agents -- often noted as having particularly severe side effects for older aged patients[19]. Psychotherapeutic agents as noted earlier are the most commonly misused drugs by physicians in a population of older aged dementia patients[2]. These psychotherapeutic agents, by way of their side effects, bring an increased risk of falls. It has also been noted in previous research that the adverse effects of psychotherapeutic agents are magnified when taken in conjunction with a large number of other medications[19]. This furthers the case for polypharmacy's contribution to the growing problem of falls in older aged adults, particularly a population suffering from dementia.

Furthermore, psychotherapeutic agents have side effects similar to that of both dementia and some autoimmune disorders, including aggressive responses, insomnia, muscle and joint pain, difficulty in thinking, loss of coordination, and motor ticks[20]. We hypothesize that psychotherapeutic agents may contribute to a thinning of the myelin layer and work to allow Tau tangles to accelerate dementia[21]. In this way psychotherapeutics may function as not only a fall trigger, but also as a dementia accelerator.

Future studies, through utilization of pharmacogenomic testing, should explore whether the relationship existing between *Number of Falls* and *Number of Medications* is due to the total number of medications (polypharmacy), or due to medication-patient mismatch. By making this differentiation,

procedures may be implemented to take out those factors which contribute to chronic falling.

Limitations of this study included a total number of participants equal to 153. In future studies with greater number of participants, statistical results can be claimed with greater certainty. A further limitation of the study was the time period of data collection. Extending the period of which the number of falls was charted from 3 months to one year would allow for the effects of *Number of Medications* and *Use of Psychotherapeutic Agents* to make themselves more exaggerated.

This research illustrates that there is a well defined relationship between the number of falls of a participant with dementia, and the number of medications that that participantis currently prescribed. Furthermore, this relationship between falls is even stronger when considering the use of psychotherapeutic agents. Physicians in long term care settings should exercise caution when adding medications to a patient's treatment plan. This research suggests that there is evidential cause to further investigate psychotherapeutic agents' role in functioning as an accelerator for dementias.

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