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Prevalence of Torsades de Pointes inducing drugs usage among elderly outpatients in North Jordan Hospitals

Ahmad Al-Azayzih*, Sara Gharaibeh, Anan S. Jarab, Tareq L. Mukattash

Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid 22110, Jordan

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ABSTRACT

Background: Torsade de Pointes (TdP) is an abnormal cardiac rhythm associated with a prolongation of QT interval. Although in most cases it spontaneously returns to the normal rhythm, TdP can lead to sudden cardiac death. Medications are the main cause of QT-prolongation and subsequent TdP flare, even though the exact mechanism of why some people evoke TdP but others do not is still unknown. It is evident that elderly patients are more susceptible to experience drug's side effects especially with chronically used medications.

Objectives: To describe the pattern of prescribing drugs with risk of Torsade's de Pointes among elderly patients who were visiting different outpatient clinics in North Jordan Hospitals.

Methods: All patients who were aged ≥ 65 years old and were visiting outpatient clinics in King Abdullah University Hospital (KAUH) and Princess Basma Hospital (PBH) through December 2016 were included in the study. A total of 5319 patients' dispensing records were collected and analyzed for the prevalence of drug-induced TdP using both Microsoft Excel and the SPSS statistical software.

Results: A total of 5319 patients were included in the study, more than half (58.5%, $n = 3114$) of patients were consuming drugs with risk of TdP. Almost half (49.4%, $n = 1539$) of these patients were women. The majority of patients (62.3%, $n = 1939$) were using only one drug with TdP risk. However, other patients were found to take five or six different TdP-inducing drugs. Excluding age and gender, 94.3% ($n = 2937$) of patients who were using TdP-inducing drugs had at least one additional risk factor of inducing TdP.

Conclusion: High usage of TdP-inducing drugs among geriatric patients in North Jordan demonstrated the urgent need for increasing awareness of TdP's risk induced by commonly prescribed medications.

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1. Introduction

Globally, cardiovascular diseases were found to be the cause of 30% of deaths; sudden cardiac deaths (SCD) account for 40–50% of all cardiovascular death cases and for 15–20% of all deaths (Mehra, 2007, Hayashi et al., 2015). Sudden cardiac death is the medical term for the unexpected death that occurs when the heart stops beating (Jentzer et al., 2015). It is challenging to determine the pre-

dominant cause of SCD, especially because 40% of known SCD cases were clinically unwitnessed (de Vreede-Swagemakers et al., 1997). However, most hospitalized SCD cases were attributed to lethal ventricular arrhythmia, or more precisely to ventricular fibrillation (V-fib) (Mehra, 2007). V-fib is the irregular rhythm that makes the heart vibrates rather than pulsate. These vibrations are not strong enough to pump blood throughout the body, hence clinical death.

However, not all ventricular arrhythmias will inevitably proceed to SCD. Torsades de pointes (TdP), for example, is a distinctive type of ventricular arrhythmia that usually self-terminates, although it is still possible for it to develop into SCD. The factors that cause some forms of ventricular arrhythmia but not others to progress toward SCD are still being debated in medical research and literature (Dessertenne et al., 1966). TdP is considered to be the result of unpredictable Long QT syndrome (LQTS) complications. LQTS is an asymptomatic cardiac condition that is sometimes acquired as a result of taking interacting medications or, less commonly, is the result of inherited gene mutations

* Corresponding author at: Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. BOX 3030, Irbid 22110, Jordan.

E-mail address: aaazayzih@just.edu.jo (A. Al-Azayzih).
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(Jackman et al., 1988). Various medications like anti-arrhythmia, anti-microbial, and anti-psychotic medications as well as some diuretics are known to carry the risk of inducing LQTS through various mechanisms (Ponte et al., 2010). Despite this, not all patients who consume these medications will necessarily develop TdP (Roden, 2004). Other risk factors typically play a role in such cases. There are two categories of risk factors for developing TdP: non-modified risk factors (in this case, female gender, advanced age, heart diseases, thyroid diseases, renal dysfunctions) and modified risk factors (high medication dosages, polypharmacy, digitalis therapy, electrolyte imbalances induced by diuretics) (Jackman et al., 1988; Roden, 2004).

In response to the increasing demand of reducing adverse drug events, Credible Meds (www.crediblemeds.org) has established a list of drugs that increase risk of TdP. They classified these into drugs with “known risk,” “possible risk,” or “conditional risk” of TdP. Various reports have shown that elderly patients who were using medications with risk of TdP (especially those categorized as known or possible risk) were at higher risk of mortality compared to elderly patients who were not using these medications. (De Ponti et al., 2002; Aichhorn et al., 2006; Danielsson et al., 2016; Franse et al., 2000).

1.1. Aim of the study

The current study aimed to determine the prevalence of drug-induced TdP and the variables associated with it among elderly patients (>65 years old) who visited the outpatient clinics in north of Jordan.

1.2. Ethics approval

Approval of the study protocol was granted by the Institutional Review Boards of Jordan University of Science and Technology and all the study hospitals (Grant number of 20160482).

2. Methods

2.1. Study design and data collection

A multicenter descriptive cross-sectional study was conducted in the outpatient clinics of King Abdullah University Hospital (KAUH) and Princess Basma Hospital (PBH) through December 2016. The patients were included in the study if they were 65 years old or more and if they received at least one medication. A total of 3175 and 2152 patient's dispensing records were collected from PBH, KAUH respectively. Eight patients were excluded as they had their medications dispensed from both hospitals and therefore a total number of 5319 patients were included in the present study. Data was gathered by collecting patients' medication records that have demographic data, clinical characteristics and routinely prescribed medications for all patients with the age of 65 and over.

Drugs that induced TdP were identified and classified into three categories according to the most updated credible Meds QT-Drug List (May 17, 2017) (Appendix A). These categories are established depending on availability of evidences. First, known risk category which contains all drugs with substantial evidences that support the conclusion of causing QT prolongation and are associated with a risk of TdP when used as directed in the labeling. Second, possible risk category which contains all drugs with substantial evidences that support the conclusion of causing QT prolongation but with insufficient evidences that these drugs, when used as directed in the labeling, have a risk of causing TdP. Third, conditional risk category which contains all drugs with substantial evidences that

support the conclusion of causing QT prolongation and are associated with a risk of developing TdP, but only under certain known conditions (e.g. excessive dose or overdose, or being the index or interacting agent in a drug–drug interaction).

Risk factors that predispose to TdP were identified depending on patients medication's records according to the following assumptions:

1. Cardiovascular disease. We assumed that patients who used Beta blockers; Carvedilol, Atenolol, Bisoprolol (excluding patients who dispensed them from Psychology and Neurology Clinic) or anti-anginal drugs (Nitrates, Calcium channel blocker (CCB), Ranolazine) or inotropic agents (Digoxin) had experienced a cardiovascular event (Kaye et al., 2013; Letsas et al., 2007).
2. Digitalis usage (Roden, 2004).
3. Electrolytes imbalance. We assumed that patients who used diuretics (loop diuretics, thiazide diuretics, carbonic anhydrase inhibitors, potassium sparing diuretics) had a high risk of electrolytes imbalance (Letsas et al., 2007).
4. End-Stage Renal Disease (ESRD). We used last serum creatinine reading to calculate eGFR using MDRD formula to estimate patient's renal function. Patients with eGFR less than 15 mg/dL were considered to have ESRD (Letsas et al., 2007; Kaye et al., 2013).
5. Thyroid disease. We assumed that patients who used thyroid hormones or anti-thyroid medications (carbimazole) have experienced thyroid disease (Letsas et al., 2007; Kaye et al., 2013).
6. Polypharmacy (minor polypharmacy 2–4 drugs; major polypharmacy ≥ 5) (Letsas et al., 2007, Bjerrum et al., 1997; Hayes et al., 2007)
7. Use of more than one drug-induced TdP (Moreno-Gutierrez et al., 2016; Drew et al., 2010).

2.2. Statistical analysis

Data was collected and analyzed using both Microsoft Excel and the SPSS (version 23). Descriptive statistics were used to describe demographics and other characteristics of patients. Categorical and continuous variables were expressed as frequency (percentage) and mean \pm SD, respectively. The primary outcome variable is the prevalence of TdP associated drugs. Patients' data were entered into a database in order to obtain following variables including Patient's demographic information (gender, age), the prevalence of drug-induced Torsade de Pointes, the percentage of each drug-induced TdP category, the pattern of drug-induced TdP prescribing from each outpatient clinics independently and the percentage of each risk factor that patients using at least one TdP-inducing drug may have.

3. Results

3.1. Demographic data

A total of 5319 patients were included in the study, 2152 patients from KAUH, 3175 patients from PBH were considered to participate in the current study. Eight patients, who had their medications dispensed from both hospitals, were excluded from the study. Approximately, half of the participants (48%; $n = 2554$) were female patients. The mean age was 73.31 years; 63.2% ($n = 3364$) of them were 65–74 years of age, 30.8% ($n = 1636$) of them were 75–84 years of age and 6% ($n = 319$) of them were 85 years of age and older.

3.2. TdP- inducing drugs

More than half (58.5%) of these patients (n = 3114) were consuming at least one drug of 48 different drugs with risk of TdP. (Appendix B) The total number of dispensed TdP inducing drugs was 4584 drugs. The mean number of TdP-inducing drugs usage among those patients was 1.47 (range 1–6). The majority of patients (62.3%, n = 1939) were using one drug with TdP risk, 29.8% (n = 929) were using two drugs with TdP risk, 6.6% (n = 207) were using three drugs and 1.1% (n = 33) were using four drugs. Moreover, 5 patients were consuming five drugs with TdP risk and one patient was taking six different drugs with TdP risk (Fig. 1).

Among Credible Meds TdP risk classification, 68.5% (n = 3140) of the TdP-inducing drugs used among these patients were classified in conditional risk category, Lansoprazole was the most frequently drug prescribed (20.7%, n = 948). Drugs with possible risk comprised of 16.6% (n = 760) in which Famotidine accounted for 10.8% (n = 496). Within known risk category (14.9%, n = 684) antibiotics took the most prescribed TdP-inducing drugs, of these Ciprofloxacin (6%, n = 277) and Azithromycin (2.7%, n = 125). The prescription pattern of the most prescribed TdP-inducing drugs is shown in (Table 1).

A total of 702 patients were using at least two drugs with conditional risk in which 38.6% of these patients were 75 years of old or more. Furthermore, 27 patients were using at least two drugs with known risk in which 44.1% of them were equal or older than 75 year and 63% of them were consuming more than two drugs with defined risk of TdP.

Gastrointestinal clinics had the highest percentage (41.6%, n = 1909) in prescribing TdP-inducing drugs followed by cardiology clinics with 33.2% (n = 1522). On the other hand neurology and psychology Clinics and urology clinics had the lowest percentage in prescribing TdP-inducing drugs (Table 2). Furthermore, drugs with conditional risk of inducing TdP were the most prescribed in all mentioned clinics except for urology clinics where drugs with possible risk were the most prescribed TdP- inducing drugs as shown in (Fig. 2).

3.3. Risk factors

In patients who consumed at least one TdP-inducing drug (n = 3114), 94.3% of them (n = 2937) had at least one additional

Table 1

Prescriptions pattern of the most prescribed TdP-inducing drugs among geriatric patients in North Jordan. Drugs with TdP risk are identified according to CredibleMeds website (www.crediblemeds.org).

Total number of TdP inducing drugs n = 4584		
TdP-inducing drugs (%)	n	%
Known risk of TdP	684	14.9
Ciprofloxacin	277	6.0
Azithromycin	125	2.7
Clarithromycin	72	1.6
Levofloxacin	63	1.4
Amiodarone	38	0.8
Possible risk of TdP	760	16.6
Famotidine	496	10.8
Alfuzosin	119	2.6
Tizanidine	45	1.0
Tolterodine	30	0.7
Flupentixol	23	0.5
Conditional risk of TdP	3140	68.5
Lansoprazole	948	20.7
Furosemide	724	15.8
Hydrochlorothiazide	474	10.3
Omeprazole	378	8.2
Indapamide	285	6.2

Table 2

Prescribing pattern of TdP-inducing drugs according to the clinics visited by geriatric patients in North Jordan.

Total number of drugs n = 4584		
CLINIC	n	%
Gastrointestinal	1909	41.6
Cardiology	1522	33.2
Neurology & Psychology	248	5.4
Urology	191	4.2
Others	714	15.6

risk factor of inducing TdP excluding age and gender (table 3), the mean of risk factors in this population was 2.41 (range 1–6). 48.6% (n = 1514) of patients had one to two risk factors, 41.8% (n = 1302) had three to four risk factors and 3.9% (n = 121) had five to six risk factors as shown in (Fig. 3). Major Polypharmacy

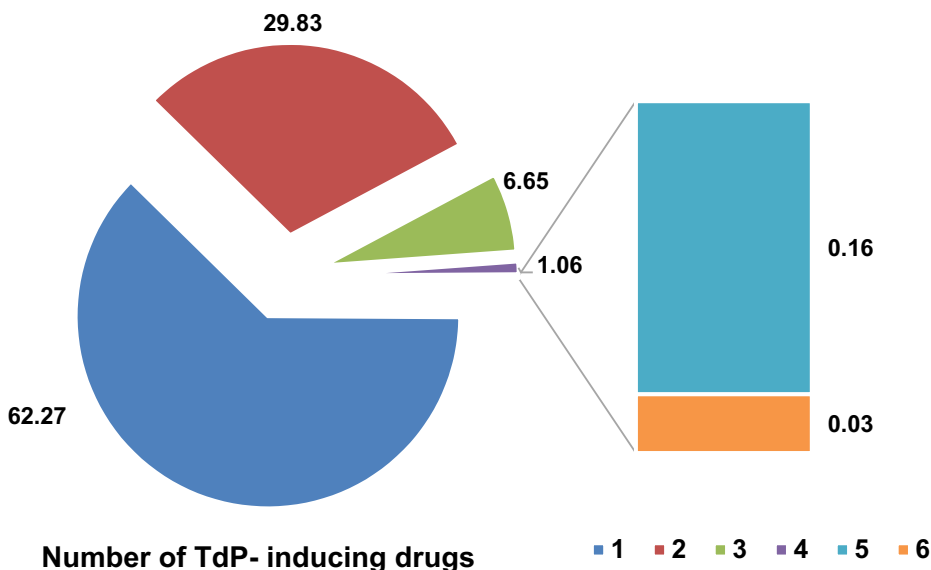
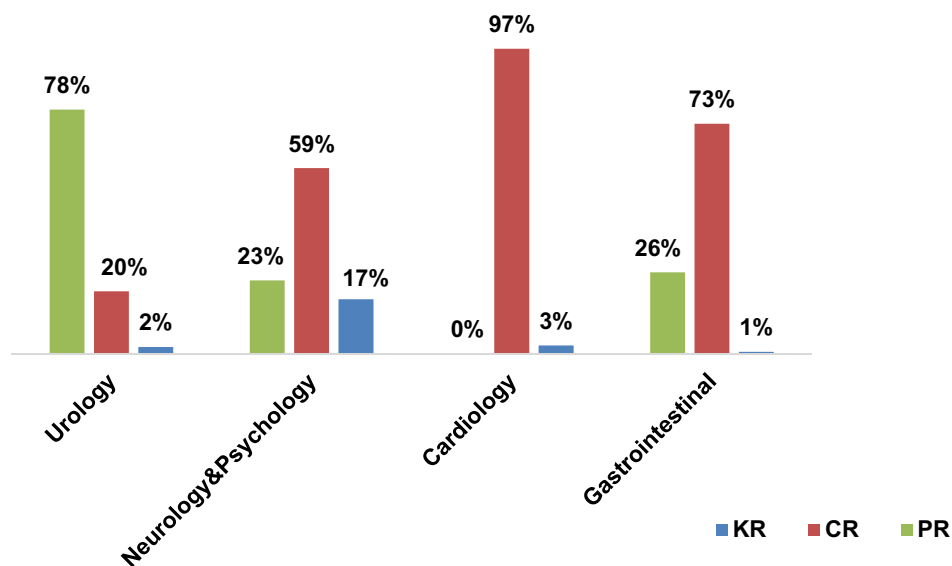


Fig. 1. Prevalence of drug-induced TdP according to the number of prescribed medications.



CR: conditional risk, KR: known risk, PR: possible risk

Fig. 2. Distribution of TdP risk categories according to the visited clinics among geriatric patients in north Jordan. CR: conditional risk, KR: known risk, PR: possible risk.

Table 3

Prevalence of TdP- risk factors among geriatric patients in North Jordan.

Risk factor	Sex				Age						
	Female		Male		65–74		75–85		>=85		
	n	%	n	%	n	%	n	%	n	%	
Cardiovascular diseases	n = 1732	899	51.9	833	48.1	1110	64.1	533	30.8	89	5.1
Electrolytes imbalance	n = 1389	767	55.2	622	44.8	870	62.6	445	32	74	5.3
Major Polypharmacy	n = 2122	1101	51.9	1021	48.1	1373	64.7	650	30.6	99	4.7
Minor Polypharmacy	n = 789	340	43.1	449	56.9	467	59.2	265	33.6	57	7.2
Thyroid Diseases	n = 141	106	75.2	35	24.8	97	68.8	37	26.2	7	5
Digitalis Use	n = 104	52	50	52	50	62	59.6	34	32.7	8	7.7
ESRD	n = 59	32	54.2	27	45.8	34	57.6	23	39	2	3.4
More than one TdP-inducing drug	n = 1171	635	54.2	536	45.8	724	61.8	380	32.5	67	5.7

ESRD: End Stage Renal Disease.

(n = 2122) was the most common risk factor among patient taking at least one TdP-inducing drug followed by cardiovascular diseases (n = 1732), other risk factors are shown in (Fig. 4). Moreover, TdP-inducing drugs with conditional risk category were the most prescribed among all risk factors as shown in (Fig. 5).

All patients who were using at least three drugs with defined risk of TdP (n = 246), had at least two additional risk factors (excluding age and gender). More than the half of these patients (n = 135, 54.9%) had additional Four risk factors. Furthermore, 43.1% of them were in the age 75 years old or more.

4. Discussion

The current study is the first report conducted in Jordan to demonstrate the alarming need for increased awareness of the risk of TdP induced by chronically-used medications prescribed to elderly outpatients in North Jordan. Our study focused on the geriatric population, as age is considered an independent risk factor for inducing LQTS and TdP. Assessing such problems will help to increase awareness among clinicians about the common TdP-inducing medications. This study highlights the importance of establishing extensive pharmaceutical care for the geriatric pop-

ulation with the aim of improving health outcomes and quality of life for elderly patients.

Studies concerning TdP-inducing drugs and their prescription patterns are increasingly being conducted around the world. In the U.S., a study with a total population of 5 million outpatients demonstrated that 1.1 million patients were dispensed a total of 4.4 million prescriptions of TdP-inducing drugs (Curtis et al., 2003). Another study conducted on 525,498 elderly patients in Colombia showed that 10.6% of these patients were using at least one drug that carried a risk of contributing to TdP (Moreno-Gutierrez et al., 2016). Our current study also demonstrated a high usage of TdP-inducing drugs among elderly outpatients in North Jordan; 58.5% of patients were consuming drugs that carry the risk of TdP.

Moreno Guterrez et al found that 60.1% of geriatric outpatients were using hydrochlorothiazide, a TdP-inducing drug which Credible Meds placed in the “conditional risk” category (Moreno-Gutierrez et al., 2016). In our study, the most dispensed TdP-inducing drug was lansoprazole (20.7%), which is also classified as “conditional risk.” Another study conducted in Sweden reported higher mortality rates in geriatric patients who were using TdP-inducing drugs with “known” and “possible” risks than

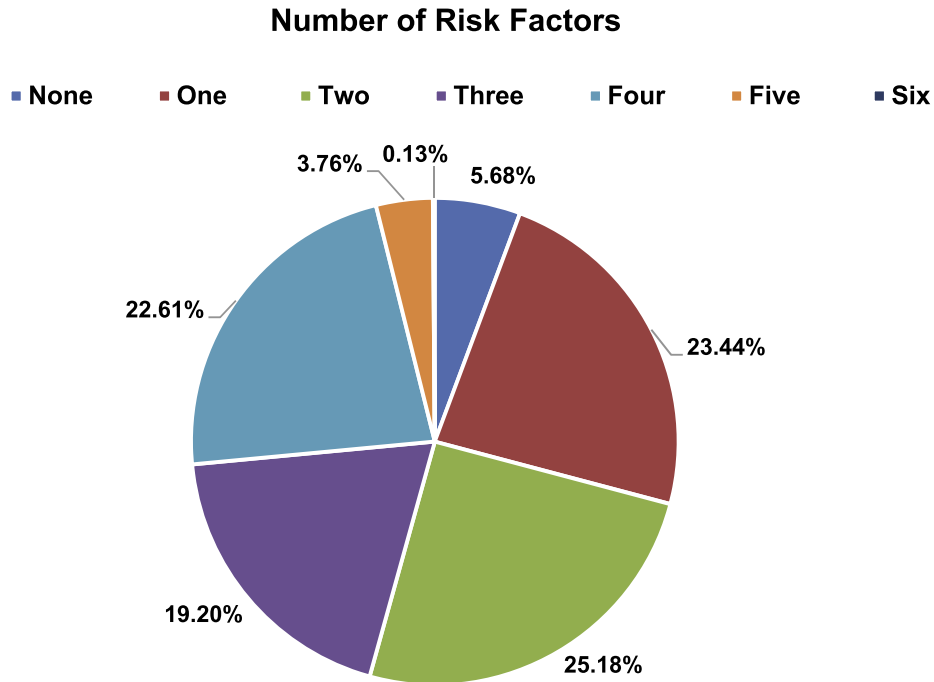


Fig. 3. The number of risk factors associated with inducing TdP in elderly outpatients consuming at least one TdP-inducing drug in North Jordan.

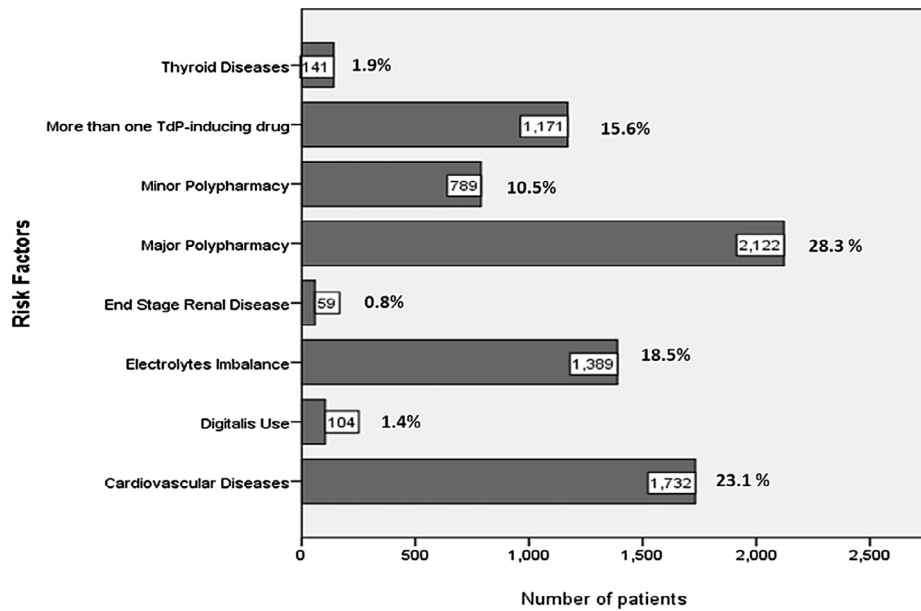


Fig. 4. Distribution of risk factors for Torsade de Pointes in patients taking at least one TdP-inducing drug (Total number of patients and percentages are presented per each risk factor).

those using TdP-inducing drugs labeled “conditional risk” or not using a TdP-inducing drug at all (Danielsson et al., 2016). This finding couldn’t be taken for granted because only patients who were visiting psychology clinics were included in the Sweden study. Moreover, 94.3% of patients for whom TdP-inducing drugs in the “conditional risk” category were the most prescribed among all risk factor groups also had at least one additional risk factor, excluding age and gender. Therefore, one can assume that patients who used TdP-inducing drugs which were categorized as “conditional risk” drugs may actually have these other risk conditions.

In our study, 684 (14.9%) TdP-inducing drugs with “known risk” were dispensed to 684 (14.9%) of geriatric patients, while drugs with “possible risk” were distributed to 760 (16.6%) of geriatric patients. These findings demonstrate a lack of awareness among physicians about the need to obviate the use of TdP-inducing drugs that are considered “known” or “possible” risks among the geriatric population, when possible. Moreover, these findings revealed the lack of intensive concern needed for very old patients (75 years old or more) as this population accounts for 44.1% of patients taking at least two drugs with known risk of TdP and 43.1% of patients

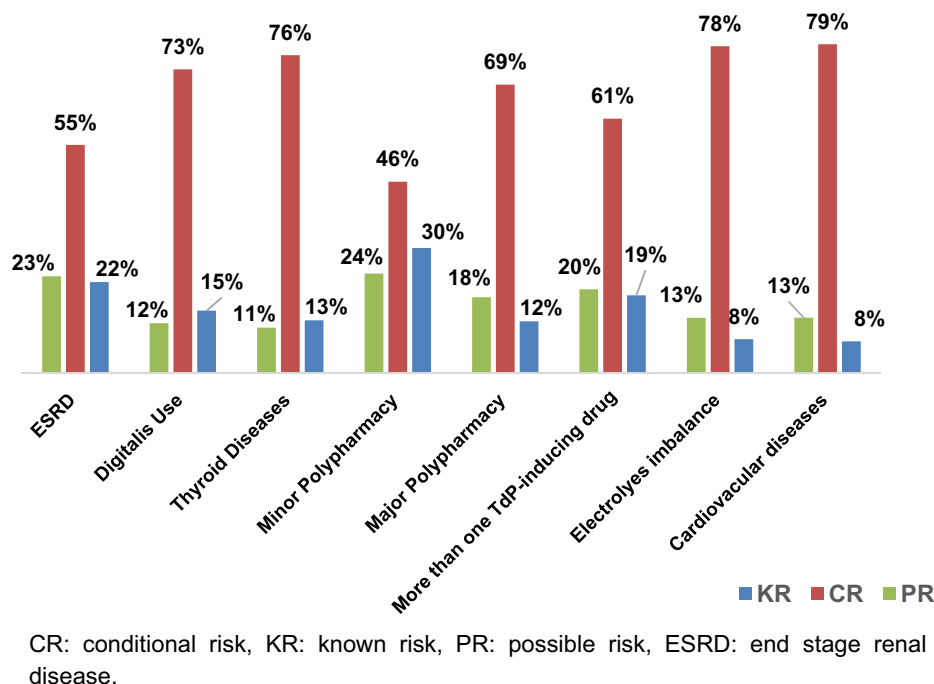


Fig. 5. TdP risk categories percentages according to the risk factors among geriatric patients in north Jordan. CR: conditional risk, KR: known risk, PR: possible risk, ESRD: end stage renal disease.

taking at least three TdP-inducing drugs with at least two additional risk factors.

In order to determine why so many patients took drugs that increased their risk of developing TdP, we have analyzed the pattern of TdP-inducing drug dispersal in the most commonly visited outpatient clinics independently. The current study revealed that 41.6% of dispensed TdP-inducing drugs were prescribed from GI clinics even when other alternative drugs without TdP risk were available. This highlights the lack of awareness about the risk that certain medications carry and suggests a lack of coordination between the prescribing physicians and the pharmacists. Moreover, 33.2% of dispensed TdP-inducing drugs were prescribed from cardiovascular clinics, among which diuretics were predominant. Diuretics are strongly associated with electrolyte imbalance and can often induce LQTS or TdP risk, as a retrospective study in France demonstrated. This study, which examined geriatric patients across ten years, found that diuretics users accounted for 44.8% of TdP cases and 32.1% of LQTS cases (Goutelle et al., 2014). These findings emphasized the need for regular monitoring of electrolyte levels in patients who are utilizing diuretics and diuretic-like medications.

The present research revealed that 15.6% of dispensed TdP inducing drugs were antimicrobial drugs, of which 89.8% were classified within known TdP risk category. Consistent with current research findings, a study conducted in the US demonstrated that 47.4% of all TdP-inducing drugs that are used by more than 1 million adult patients were macrolide antibiotics (clarithromycin and erythromycin) which are TdP-inducing drugs in the “known risk” category (Curtis et al., 2003). However, further studies regarding acute and chronic use of antimicrobial medications in geriatric patients is warranted.

In this study, major polypharmacy (defined as dispensing 5 medications or more) was the most common risk factor; approximately half of patients who were treated by at least 5 medications were using more than one TdP-inducing drug. We suggest that the lack of communication between different clinics resulted in major

polypharmacy. In fact, many patients were visiting more than one clinic in one month, which calls attention to the important role of pharmacists in assessment and optimization of the pharmacotherapy. It also suggests an increased need for efforts that consider patient monitoring after discharge in order to decrease or prevent the potential risk of LQTS and TdP. A study conducted in Germany showed that 60% of patients documented with drug-induced LQTS were treated in outpatient clinics (Sarganas et al., 2014).

Geriatric patients in North Jordan who are visiting outpatient clinics are exposed to high risk of cardiac sudden death due to incurious usage of drugs that increase risk of LQTS and TdP when physicians fail to consider concurrent risk factors in those patients. Moreover, the lack of regular electrolyte monitoring, ECG monitoring, and the lack of communication between the pharmacy and other clinic departments may contribute to poor health outcomes for elderly patients in Jordan. This increase the impact of the work and strengthened the importance of raising awareness by clinicians as preventive strategy and ensures the urgent need to institute geriatric clinical pharmacy services, which should provide care for all elderly outpatients who are prescribed with at least one drug. This specific medical care will examine the following aspects: The presence of any drug with TdP risk, the presence of any TdP risk factors (cardiovascular disease, electrolytes imbalance, digitalis use, thyroid disease, poly-pharmacy, ESRD, more than one TdP-inducing drug usage), the availability of alternative medications without risk of TdP, the presence of any other drug-drug interactions.

The suggested geriatric clinical pharmacy model shown in (Fig. 6) summarizes these aspects. It specifically assesses any risk of inducing LQTS/TdP and effectively gives recommendations for improving clinical pharmacy service for elderly patients.

This study has some limitations. The current study didn't include drugs to be avoided in patients with congenital long QT prolongation, since we don't have accurate estimation of the prevalence in our study sample. The current study was conducted in North Jordan, which might not represent the whole picture for

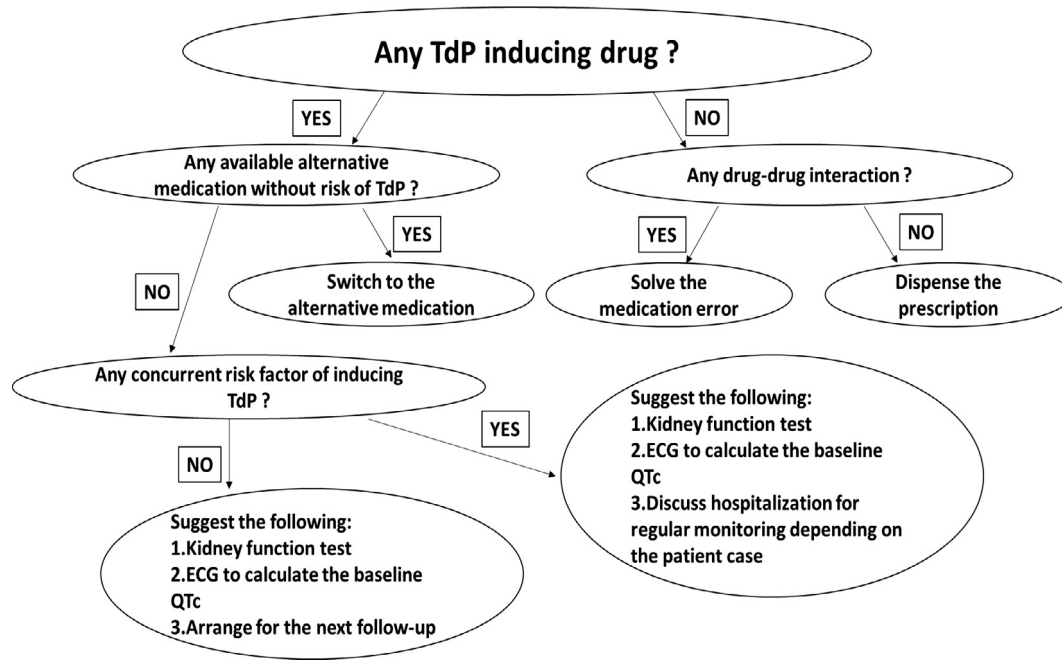


Fig. 6. Suggested algorithm to help physicians and clinical pharmacists to avoid unnecessary prescribing of TdP-inducing medication in elderly patients.

the prescribing behaviour in other geographical areas hospitals in Jordan, Also some of the TdP risk factors were not assessed in our report due to the limited nature of our data, but on the other hand we have identified the majority of those risk factors which are highly associated with TdP risk. Finally, Because of the nature of data, this drug utilization study did not analyze outcome data (hospitalization for arrhythmia, TdP occurrence, sudden cardiac death, etc. . .) or other identified risk factors. However, this study focused on the most internationally accepted risk factors (Jackman et al., 1988; Ponte et al., 2010).

5. Conclusion

Our Study showed a high prescribing of TdP-inducing drugs among geriatric patients in North Jordan area. These findings suggest the urgent need for increasing awareness of TdP's risk induced by commonly prescribed medications. Hence we suggest instituting geriatric clinical pharmacy service that detect and solve drug induced side effect, in our case TdP inducing drugs. Hence, we have suggested a algorithm (Fig. 6) to simplify the preventative strategies in how to avoid TdP-inducing drug risk and to be utilized as guidance for clinical settings to avoid decrease the prevalence of TdP risk among elderly patients.

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Conflict of interest

The authors declare no conflict of interest does exist.

Appendix A. List of all drug associated with long QT interval prescribed by outpatient clinics in North Jordan.

Generic name	Generic name
Alfuzosin (PR)	Levofloxacin (KR)
Amantadine (CR)	Levomopromazine (KR)
Amiodarone (KR)	Levomethadyl acetate (KR)
Amisulpride (CR)	Levosulpiride (KR)
Amitriptyline (CR)	Lithium (PR)
Amphotericin B (CR)	Loperamide (CR)
Anagrelide (KR)	Melperone (PR)
Apomorphine (PR)	Mesoridazine (KR)
Aripiprazole (PR)	Methadone (KR)
Arsenic trioxide (KR)	Metoclopramide (CR)
Arteminol+piperazine (PR)	Metronidazole (CR)
Asenapine (PR)	Mifepristone (PR)
Astemizole (KR)	Mirabegron (PR)
Atazanavir (CR)	Mirtazapine (PR)
Atomoxetine (PR)	Moexipril/HCTZ (PR)
Azithromycin (KR)	Moxifloxacin (KR)
Bedaquiline (PR)	Necitumumab (PR)
Bendamustine (PR)	Nelfinavir (CR)
Bendroflumethiazide or bendrofluazide (CR)	Nicardipine (PR)
Bepidil (KR)	Nilotinib (PR)
Bortezomib (PR)	Norfloxacin (PR)
Bosutinib (PR)	Nortriptyline (PR)
Buprenorphine (PR)	Nusinersen (PR)
Capecitabine (PR)	Ofloxacin (PR)
Ceritinib (PR)	Olanzapine (CR)
Chloral hydrate (CR)	Omeprazole (CR)
	Ondansetron (KR)

Appendix A (continued)

Generic name	Generic name
Chloroquine (KR)	Osimertinib (PR)
Chlorpromazine (KR)	Oxaliplatin (KR)
Cilostazol (KR)	Oxytocin (PR)
Ciprofloxacin (KR)	Paliperidone (PR)
Cisapride (KR)	Panobinostat (PR)
Citalopram (KR)	Pantoprazole (CR)
Clarithromycin (KR)	Papaverine HCl (Intra-coronary) (KR)
Clomipramine (PR)	Paroxetine (CR)
Clozapine (PR)	Pasireotide (PR)
Cocaine (KR)	Pazopanib (PR)
Crizotinib (PR)	Pentamidine (KR)
Cyamemazine (PR)	Perflutren lipid microspheres (PR)
Dabrafenib (PR)	Perphenazine (PR)
Dasatinib (PR)	Pilsicainide (PR)
Degarelix (PR)	Pimavanserin (PR)
Delamanid (PR)	Pimozide (KR)
Desipramine (PR)	Pipamperone (PR)
Dexmedetomidine (PR)	Posaconazole (CR)
Diphenhydramine (CR)	Probucol (KR)
Disopyramide (KR)	Procainamide (KR)
Dofetilide (KR)	Promethazine (PR)
Dolasetron (PR)	Propofol (KR)
Domperidone (KR)	Prothipendyl (PR)
Donepezil (KR)	Quetiapine (CR)
Doxepin (CR)	Quinidine (KR)
Dronedarone (KR)	Quinine sulfate (CR)
Droperidol (KR)	Ranolazine (CR)
Efavirenz (PR)	Ribociclib (PR)
Eribulin mesylate (PR)	Rilpivirine (PR)
Erythromycin (KR)	Risperidone (PR)
Escitalopram (KR)	Ritonavir (CR)
Esomeprazole (CR)	Romidepsin (PR)
Ezogabine (Retigabine)(PR)	Roxithromycin (KR)
Famotidine (PR)	Saquinavir (PR)
Felbamate (PR)	Sertindole (PR)
Fingolimod (PR)	Sertraline (CR)
Flecainide (KR)	Sevoflurane (KR)
Fluconazole (KR)	Solifenacin (CR)
Fluoxetine (CR)	Sorafenib (PR)
Flupentixol (PR)	Sotalol (KR)
Fluvoxamine (CR)	Sparfloxacin (KR)
Furosemide (frusemide) (CR)	Sulpiride (KR)
Galantamine (CR)	Sultopride (KR)
Garenoxacin (CR)	Sunitinib (PR)
Gatifloxacin (KR)	Tacrolimus (PR)
Gemifloxacin (PR)	Tamoxifen (PR)
Granisetron (PR)	Telaprevir (CR)
Grepafloxacin (KR)	Telavancin (PR)
Halofantrine (KR)	Telithromycin (PR)
Haloperidol (KR)	Terfenadine (KR)
Hydrochlorothiazide (CR)	Terlipressin (KR)
Hydrocodone - ER (PR)	Terodiline (KR)
Hydroxychloroquine (CR)	Tetrabenazine (PR)
Hydroxyzine (CR)	Thioridazine (KR)
Ibogaine (KR)	Tiapride (PR)
Ibutilide (KR)	Tizanidine (PR)
Iloperidone (PR)	Tolterodine (PR)

Appendix A (continued)

Generic name	Generic name
Imipramine (melipramine) (PR)	Torasemide (CR)
Indapamide (CR)	Toremifene (PR)
Isradipine (PR)	Trazodone (CR)
Itraconazole (CR)	Trimipramine (PR)
Ivabradine (CR)	Tropisetron (PR)
Ketanserin (PR)	Vandetanib (KR)
Ketoconazole (CR)	Vardenafil (PR)
Lansoprazole (CR)	Venlafaxine (PR)
Lapatinib (PR)	Vorinostat (PR)
Lenvatinib (PR)	Ziprasidone (CR)
Leuprolide (PR)	Zotepine (PR)

CR: conditional risk, KR: known risk, PR: possible risk.

Appendix B. List of all drugs associated with long QT-interval prescribed by outpatient clinics in North Jordan Hospitals. CR: conditional risk, KR: known risk, PR: possible risk.

Generic name	Generic name
Alfuzosin (PR)	Hydrochlorothiazide (CR)
Amantadine (CR)	Hydroxychloroquine (CR)
Amiodarone (KR)	Imipramine (melipramine)(PR)
Amisulpride (CR)	Indapamide (CR)
Amitriptyline (CR)	Lansoprazole (CR)
Azithromycin (KR)	Levofloxacin (KR)
Capecitabine (PR)	Loperamide (CR)
Ciprofloxacin (KR)	Metoclopramide (CR)
Citalopram (KR)	Metronidazole (CR)
Clarithromycin (KR)	Mirtazapine (PR)
Clomipramine (PR)	Olanzapine (CR)
Clozapine (PR)	Omeprazole (CR)
Domperidone (KR)	Ondansetron (KR)
Erythromycin (KR)	Quetiapine (CR)
Escitalopram (KR)	Risperidone (PR)
Esomeprazole (CR)	Sertraline (CR)
Famotidine (PR)	Solifenacin (CR)
Flecainide (KR)	Sulpiride (KR)
Fluconazole (KR)	Tacrolimus (PR)
Fluoxetine (CR)	Tamoxifen (PR)
Flupentixol (PR)	Terfenadine (KR)
Fluvoxamine (CR)	Tizanidine (PR)
Furosemide (frusemide)(CR)	Tolterodine (PR)
Haloperidol (KR)	Venlafaxine (PR)

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