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Drug Prescribing in Older Patients

Graduate thesis



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This graduate thesis was made at the Department of Clinical Pharmacology and Therapeutics, Rebro, University Hospital Centre, Zagreb, Croatia, mentored by Professor Robert Likic, and was submitted for evaluation in the academic year 2019/2020.

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List of abbreviations:

- ADE: Adverse Drug Events
- OTC: Over The Counter
- NSAID: Non-steroidal Anti-inflammatory
- START: Screening Tool to Alert Doctors to the Right Treatment

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1.0 - Summary

Drug prescribing in older patients, Marko L. Boskovic. Poor prescribing is a common occurrence, notably relevant in settings with at-risk patients. Patients with multiple comorbidities require multiple drug therapies, establishing fertile soil for the manifestation of adverse drug events. As organ function decreases in older patients, drug doses oftentimes are failed to be prescribed at an appropriate level. The combination of elevated doses and unnecessary prescriptions puts endangered patients at further risk for developing avoidable adverse events. In order to protect vulnerable patients, strides must be taken towards appropriate prescribing and dosing. When the focus of treatment is clear with defined goals, we can aim at providing a suitable regimen which adds life to the remaining years of our patients.

Key Words: Prescribing, polypharmacy, adverse drug events, geriatrics.

1.1 - Sažetak

Primjena lijekova u pacijenata starije životne dobi, Marko L. Boskovic.

Neefikasno propisivanje lijekova uobičajena je pojava, osobito relevantna u okruženjima s rizičnim pacijentima. Bolesnici s više komorbiditeta zahtijevaju višestruke terapije lijekovima, uspostavljajući plodno tlo za utjecaj štetnih lijekova. Kako opada funkcija organa kod starijih bolesnika, doze lijekova često se ne propisuju na odgovarajućoj razini. Kombinacija povišenih doza i nepotrebnih recepata stavlja ugrožene pacijente u daljnji rizik kod razvoja nuspojava koje se mogu izbjeći. Da bi se zaštitili ranjivi pacijenti, potrebno je poduzeti korake prema odgovarajućem propisivanju i doziranju. Kad je fokus liječenja jasan sa definiranim ciljevima, možemo se usmjeriti na pružanje odgovarajućeg režima koji će dodati život ostalim godinama našim pacijentima.

Ključne riječi: propisivanje, polifarmacija, štetni događaji lijekova, gerijatrija.

2.0 - Introduction

The most frequent medical intervention performed by a doctor is the writing of a prescription. Poor prescribing is unfortunately a common occurrence. Often times junior doctors who have recently graduated, are faced with this task without the privilege of years of experience to lean on. Prescription medications are often added without much deliberation and to the detriment of patients are reluctantly removed. These inefficient practices lead to a drug medley which impacts drug metabolism unpredictably. The pharmacokinetic properties of each medication are largely affected with the introduction of each new drug and why efficient prescribing practices are so important. Failing to prescribe efficiently often leads to detrimental effects, especially in patients with multiple comorbidities. In order to protect this population, close care must be taken to optimize drug therapy.

3.0 - Adverse Drug Events: Identifying the cause and removing the source

An **adverse drug event (ADE)** refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury. Adverse drug events comprise the single largest category of adverse events experienced by hospitalized patients, accounting for 19% of all injuries ^[1]. The occurrence of ADE is associated with increased hospitalization, increased morbidity and mortality, as well as a higher cost of care ^[2,3,4]. In order to decrease adverse drug events, vulnerable populations must be identified and treated with special consideration.

Older adults and patients with multiple comorbidities are at particular risk of developing ADE due to their multiple drug therapies. Renal impairment is of particular importance and can occur at any age, but becomes prominent in geriatric populations as creatinine clearance decreases in the later stages of life. With the decrease in renal clearance concentrations of drugs increase, contributing to further ADE. For patients with stable renal functions, creatinine

clearance can be estimated according to published formulas, however one must keep in mind that decreasing muscle mass in older adults leads to lower serum creatinine levels and may not accurately reflect renal function. Additional care must be given to the volume of distribution in older adults as body fat increases and muscle mass drops. A high body fat percentage in older adults leads to large drug storage reservoirs for lipophilic drugs. Combined with the expected decreased renal clearance and potentially decreased liver functionality, this undesirable combination results in the prolonged half-life of drugs and a higher plasma concentration; both of which are predisposing factors to adverse drug events. As ADE have been shown to be dose dependent [5,6], shown by multiple studies related to psychotropic drugs, a correct dose must be assigned in order to avoid high circulating drug concentration. A general rule that can be followed when prescribing medications to older adults is the initial dose should be significantly reduced and titrated up to an effective dose, all while following closely for adverse effects. Ideally doses would be adjusted in high risk patients based on creatinine clearance, CYP enzyme activity, age, weight and body fat percentage; as a common cause of ADE is failure to dose based on these

parameters [7]. With the consideration of all of the relevant parameters, serum concentrations are interrupted from accumulating to harmful concentrations. The use of mechanistic models can be used to aid clinical decision making. Multiple pharmacokinetic models are available for physicians to have a deeper consideration of the multiple changing variables.

4.0 - Polypharmacy- Less is more

Polypharmacy is defined simply as the use of multiple medications by a patient. The precise amount of medications used to define polypharmacy is variable, but usually constitutes 5-10 medications simultaneously [8]. A review in 2010 found that the average American 81-year-old takes an average of 15 different medications, ranging from 6 to 28 [9]. While poly pharmacy most often refers to prescription medication, it is also important to consider the use of over the counter drugs and herbal medications, where use has been trending upwards [10].

4.1 - Prescribing Cascades

Multiple drug therapies and drug to drug interaction often times lead to unpredictable “prescribing cascades”. Defined as, a new symptom arising as a result of multiple drug therapy being treated improperly with a new drug, resulting in an additional prescription, and additional increase in drug-drug interaction [11]. Prescribing cascades are often shown in older adults, as their multiple drug therapy offers a fertile soil for adverse effects.

One of the best recognized examples of a prescribing cascade relates to the initiation of anti-parkinsonian therapy for symptoms arising from the use of metoclopramide and antipsychotics [12-15]. The now newly added anti-parkinsonian drug can lead to new symptoms, including orthostatic hypotension and delirium; causing additional medication to be implemented, perpetuating the cascade.

In a case control study of 3512 Medicaid patients, patients who were prescribed an antipsychotic medication in the preceding 90 days were 5.4 times more likely to be prescribed anti-parkinsonian therapy than patients who had not received an antipsychotic [12]. This is an excellent example that highlights

inappropriate prescribing. A new symptom arose, and the inability to diagnose delirium as an adverse event of the antipsychotic leads to the commencement of the anti-parkinsonian therapy. Failing to review patients' prescriptions as symptoms arise predisposes them to effects of drug cascades.

4.2 - Managing Transitions in Healthcare Settings

A survey of American community dwelling adults showed that five or more medications were used by 36% of the population, while Medicare beneficiaries who had been recently discharged from acute care were prescribed an average of 14 medications ^[16], one third of which are medications that could exacerbate geriatric syndromes.

When we examine the spike in the number of drugs used from outpatient settings compared to acute in-patient care, one may identify that as patients transition back to their homes, many of the drugs prescribed in acute settings are not discontinued. Among 384 veterans, 44% were found to have at least 1 unnecessary drug therapy at the time of discharge ^[17].

Factors that contribute to these unnecessary prescriptions are “routine” medications for hospitalization such as antacids, stool softeners, benzodiazepines and the presence of multiple prescribers. When multiple physicians are contributing the the same drug regimen often drugs are added freely and removed reluctantly. Efforts must be taken to more efficiently “hand off” patients from one setting to another. Simple ways to improve setting transitions are keeping accurate medication lists and critically analyzing the drug regimen at each change in care setting. The pharmacotherapy should be critically analyzed for appropriateness and duration of treatment. Installing a check up on patients' medications commonly called “brown bag checks” provides the opportunity to prevent harm before it is done. Removing a drug who's need has run its course removes its contribution to drug to drug interaction and increases the prescribing efficiency and patient health.

4.3 - Herbal Drug Contribution to Polypharmacy

As the use of natural and herbal medications has been on a rise since 1960 as part of a larger movement towards natural, non-conventional healthcare; drug-herb interactions must be considered alongside drug-drug interactions of prescription medication. Data from the National Health Interview Survey showed that 17.7 percent of Americans had used herbal medications in the year prior ^[18] and increasing data has been showing the potential for herbal medications to cause herb-drug interactions with prescription medication ^[19]. Many herbal medications and over the counter (OTC) drugs are commonly thought to be benign in origin (such as the commonly used fish oils and probiotics). In contrast, other commonly used herbal medications show more malignant effects. The use of coenzyme Q10 and St. John's wort, commonly used over the counter drugs, show impact on the expression of liver enzymes, increasing the expression of cytochrome P450 3A4. With the increase of liver enzyme activity, the metabolism of other drugs that use the same metabolic pathway is affected. Warfarin, digoxin, protease inhibitors and oral contraceptives

and all other CYP3A4 substrates are affected, leading to faster metabolism, decreased serum concentration and eventually the failure of therapy [20-21].

Surveys have shown that the majority of patients that use herbal medications do not disclose this information to their doctors [22]. 46% of patients taking herbal medication provided that the reason why they did not share this information is that “it wasn’t important for the doctor to know”. 57% also reported that “the doctor never asked” [22].

The consideration of patients’ pharmacokinetics comes from a necessity to include all of the medications they are taking. Without considering OTC and herbal medications physicians are left in the dark regarding P450 activity and the practice of prescribing becomes guess work.

Another advantage of discussing about herbal medications is opening a dialogue about patients concerns. Many patients take herbal medications to remedy illnesses that provide stress for them. For example, upon asking the patient about herbal medication, they report the use of vitamin E, coenzyme Q10 and garlic, revealing anxiety about myocardial infarction due to family history.

Upon measuring cardiovascular risk markers and educating the patient, the unnecessary drugs may be removed, decreasing potential for herb-drug interaction.

5.0 - Medication appropriateness: (is it kind, is it true,) is it necessary

Particularly important is the consideration of medication appropriateness late in life. When reviewing current medication and when prescribing additional medication, remaining life expectancy and goals of care must be considered. For example, if a patient has a short-term life expectancy, prescribing prophylactic medication must be contested. A concept of “Time to Benefit” in relation to drug prescribing in adults with multiple comorbidities can be used when making therapeutic decisions [23].

Various criteria have been proposed towards the appropriateness of drug prescribing. A Drug Burden Index has been modelled, which incorporates drugs with anti-cholinergic activity and sedative effects, as well as incorporating the total number of medications used and daily dosing.

An increased burden was associated with anti-cholinergic and sedative drugs. Patients were often left with impaired performance on mobility and cognitive testing while taking anticholinergic drugs [24]. In particular, zolpidem was implicated in 21% of emergency department visits for ADE related to psychiatric medication in people aged 65 or older [25]. High drug burden is related to cognitive decline, a feature deeply cherished in older adults, and increase the risk of falls in residents in long term care.

In a population of 3434 men and women aged 65 or older who had no baseline signs leading to cognitive deterioration were followed for 10 years. The risk of dementia and Alzheimer's disease increased in a dose related response with use of anti-cholinergic drug classes [26]. It is important to consider the appropriateness of the anti-cholinergic drugs and other medications with a high drug burden before prescribing; and if the prescription is warranted, to take careful consideration on the dose prescribed. Alternative drugs with lower anti-cholinergic activity are available, however other adverse drug reactions outside of anti-cholinergic activity must be considered.

Concurrent with the efforts of avoiding burdensome drugs is utilizing appropriate medication. Clinicians may be better at avoiding over-prescribing inappropriate drug therapy than at prescribing indicated drug therapy. As an example, one study of older adults found that 50 percent had not been prescribed some recommended therapy, while only 3 percent were prescribed medications classified as inappropriate [27]. Another study found that over and underutilization was equally prevalent, 65 percent of patients being treated with either over or under-utilized medication, and both under and over utilization occurring in 42 percent of patients [28].

START (Screening Tool to Alert doctors to the Right Treatment) is a set of 34 validated criteria developed by a consensus of experts in geriatric pharmacotherapy, aimed at identifying potential prescribing omissions in older hospitalized patients [29]. Factors that lead to underutilization include clinicians not being aware of potential benefit, affordability and dose availability.

6.0 - Preventing Adverse Drug Events

Because chronic illness increases with advancing age, older patients are more likely to have conditions that require multiple drug therapy. The risk of an adverse event due to drug to drug interaction is substantially higher when many medications are being prescribed. As an example, the risk of bleeding with warfarin therapy increases with co-administration of selective and non-selective NSAIDs, selective serotonin reuptake inhibitors, omeprazole, lipid lowering agents, amiodarone and fluorouracil [30]. Optimizing drug therapy, through removing ineffective and inappropriate medication and decreasing drug to drug interaction is a standard approach to decrease ADE.

An analysis of a group of Italian patients, mean age 78, revealed that the number of drugs being prescribed and prior history of ADR were the strongest predictors for subsequent ADR. When comparing patients who receive 5 or fewer medications, the risk was doubled for those prescribed 5-7 medications and fourfold for those with 8 or more [31]. Each drug that can be removed from a regimen greatly decreases the risk of adverse events.

Inappropriate ordering and inadequate monitoring are the most common errors associated with preventable ADE. Again, the population at highest risk are patients in long term care settings. Steps such as using computerized decision-making aides and consulting clinical pharmacologists can be taken to avoid inappropriate ordering.

Reviewing drug therapy, especially as patients develop new symptoms provides an opportunity to correct drug cascades. Periodic review or “brown bag checks” are an essential component of medical care for an older patient. During reviews physicians must review current drug therapy for relevance, effectiveness as well as making sure patients are being adherent to their prescriptions. A medication review should consider the patients status (hepatic and renal function), potential drug to drug interaction, symptoms of polypharmacy and goals of care.

Physicians are often reluctant to stop medications, especially if they did not initiate the treatment themselves. Continuing unnecessary medications leads to increased risk for adverse events with limited therapeutic benefit. A common

example being digoxin in older adults, often prescribed where indications have not been met.

Unfortunately, there is limited research on how to effectively remove medications from a regimen. It is reasonable to gradually taper off most medication to minimize potential medical withdrawal, while monitoring for potential symptoms. Drugs that require tapering include beta blockers, gabapentin, clonidine, anti-depressants, opioids and barbiturates.

As many ADE are dose related, titrating a patient's dose to the minimum concentration necessary for therapeutic benefit is necessary to reduce drug-drug interaction. As an example, one case-controlled study in patients over 70 who received thyroid supplementation identified a correlation between risk of fracture and dose of levothyroxine [32], indicating the importance of following levels of T4 and adjusting the dose accordingly.

Considering non-pharmacologic treatment is many times overlooked. Although many patients are reluctant to abandon sedentary lifestyles, any treatment that may be non-pharmacologic is cherished.

7.0 - Conclusions

Maintaining mobility and cognitive ability is key in maintain the quality of life in older adults. Avoiding high risk drugs and continual assessment of drug regimens provides opportunities for simple inspections and corrections. Although many medications may be necessary for older patients' multiple comorbidities, small corrections along the way may be decisive in adding life to their years and years to their life.

8.0 - References and Acknowledgements

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9. Biography

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