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# The Risk of Drug-Drug Interactions with Paracetamol in a Population of Hospitalized Geriatric Patients


Section Break

# ILOs

01 Introduction

02 Hypothesis

03 Methods

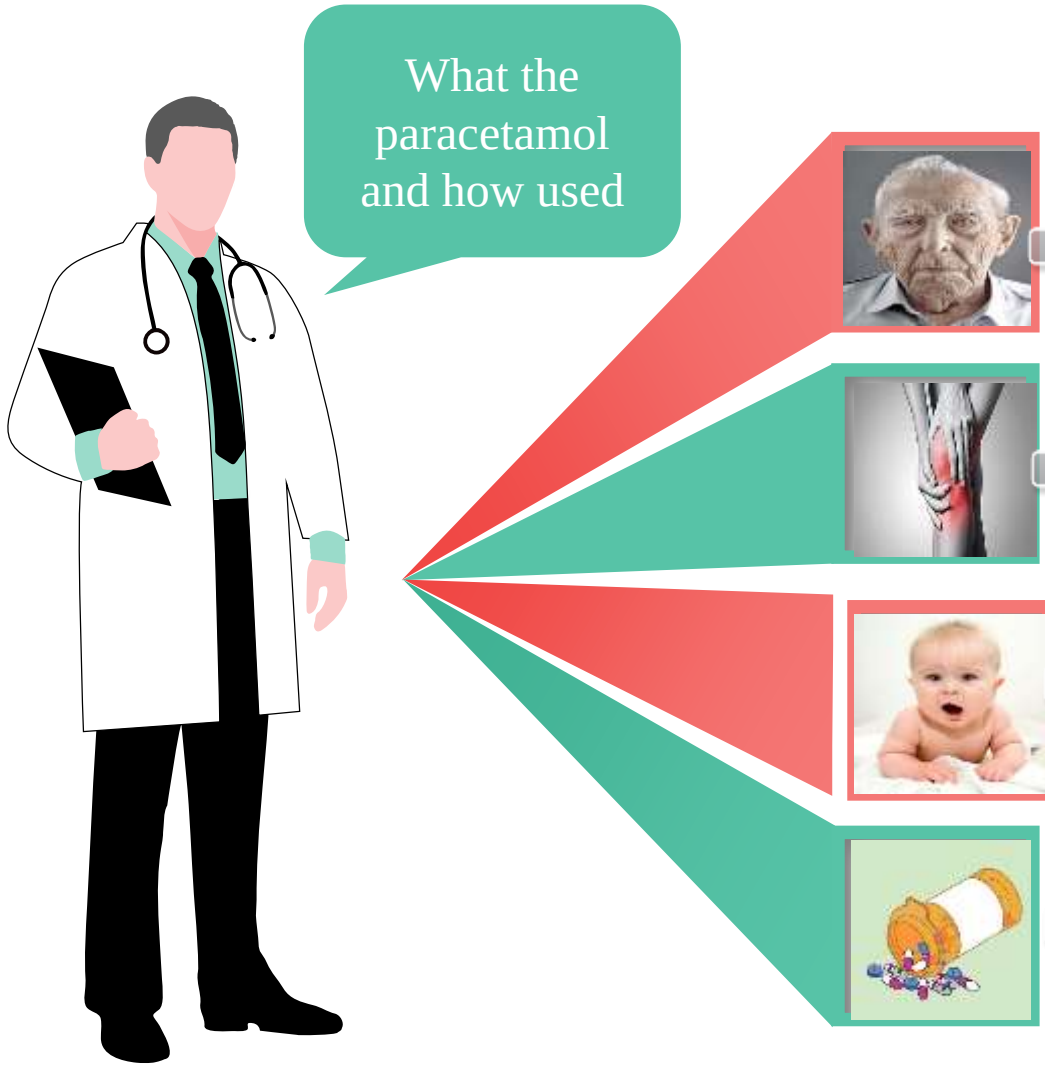
04 Result

05 Discussion

06 Conclusion

# Introduction

**The geriatric population is the fastest growing segment of our society, and this population is very heterogeneous**




1-Pain is common among the elderly since they are more likely to suffer from arthritis, bone and joint disorders, and other chronic conditions

2-Paracetamol is the most commonly used analgesic for acute and mild-to-moderate pain and is available without prescription and is the first-line analgesic in Denmark used as a maximum of four grams per day and is the first-line analgesic in Denmark used as a maximum of four grams per day

3-Elderly patients are often underrepresented or not included in clinical trials and patients admitted to departments of geriatric medicine are assumed to be more frail and in greater risk of adverse events as they often are treated with concomitant medication due to associated diseases

4-These patients are often more vulnerable due to age-related changes in pharmacokinetics and pharmacodynamics This may lead to an increased risk of acquiring potential toxicity and drug-drug interactions (DDIs)


5-Furthermore, it has been demonstrated that age and sex are important factors affecting the pharmaco kinetics of paracetamol. This results in higher concentrations of paracetamol with increased age and particularly elderly female patients

6- Despite these findings, recommendation for reducing the maximum daily dosage(4grams)in elderly patients has not been assessed to be necessary

7-Several studies have reported and investigated pDDIs with paracetamol and the anticoagulant warfarin This interaction is assumed to be a pharmacokinetic interaction- ,resulting in a reduction of warfarin clearance and hence increasing international normalized ratio (INR). This may lead to life-threatening bleeding. One such fatalDDIwasreportedinaDanishcasereportin2015,when an 83-year-old man suffering from atrial fibrillati on and back pain died from an untreatable intracerebral humor rhage

8-It has been suggested that decreased activity of CYP2E1 due to aging could increase the activity of paracetamol metabolized via CYP1A2 and CYP3A4

9- Thereby, competing with metabolism of R-warfarin which leads to inhibition of CYP2C9 that metabolizes S-warfarin. This can result in increased concentration of the S-isomer, which is five times as potent as the R-isomer . Data Management. For those who did receive any paracetamol treatment, the average administration of paracetamol per day per patient was calculated and compared toward the maximum recommended dosage. The known pDDIs with paracetamol and third-line pDDIs were identified by using the databases Micromedex (MM), interaktionsdatabasen (ID),andiron medicine(PM).Only pDDIs class Ideas major and mode rate severity MM and critical and potential problematic at ID were considered for this study.
A third-line pDDI was defined as a pDDI including the drug that also causes pDDI with paracetamol.

For instance, simvastatin-warfarin is a third-line pDDI because warfarin also can lead to a pDDI with paracetamol. This third-line pDDI may influence the pDDI between paracetamol and warfarin .A third-line drug was defined as the drug that had a pDDI with the same drug that was identified to have a PDDI with paracetamol. For instance, simvastatin is the third-line drug in the example of third-line pDDI. The patients at risk of a pDDI with paracetamol were identified, and subsequently, more thorough assessments of the patients were done. The assessments included an overall medication review of the patients' remaining medication.

# Hypothesis

Several studies have reported and investigated pDDIs with paracetamol and the anticoagulant warfarin. This interaction is assumed to be a pharmacokinetic interaction, resulting in are duction of warfarin clearance and hence increasing international normalized ratio (INR). This may lead to life-threatening bleeding. One such fatalDDIwasreportedinaDanishcasereportin2015,when an 83-year-old man suffering from atrial fibrillation and back pain died from an untreatable intracerebral haemorrhage. It has been suggested that decreased activity of CYP2E1 due to aging could increase the activity of paracetamol metabolised via CYP1A2 and CYP3A4. Thereby, competing with metabolism of R-warfarin which leads to inhibition of CYP2C9 that metabolizes S-warfarin. This can result in increased concentration of the S-isomer, which is five times as potent as the R-isomer.

# Methods

Department of Geriatric Medicine at Bispebjerg Hospital is a department with the capacity of 28 beds.
Coverage area of 400,000 citizens in part of greater Copenhagen.
Department has a yearly admission of approximately 900 patients per year .
Approximately 60% is admitted directly from the emergency department (E.R).
Data for all admitted patients during approximately 5 weeks were collected and reviewed in period.

## Screening of patient

All patients aged 65 years or more, hospitalized in the Department all were screened for registration of any prescribed or consumed paracetamol upon or during their hospitalization.
If paracetamol was used during admission, the patient's relevant biochemical values were registered diagnoses upon and under admission and chronic and temporary diagnoses were identified by reviewing the anamneses and patient files.

## Date management

Percentage of the patients receiving any treatment with paracetamol was calculated, including both the number of regular medications and PRN medications the average administration of paracetamol per day per patient was calculated and compared toward the maximum recommended dosage.

# Methods

**Known pDDIs with paracetamol and 3th line pDDIs** were identified by using the databases : *Micromedex* (MM), interaktionsdatabasen (ID), and *pro.medicin* (PM).

- **Only pDDIs classified as**

**Major and moderate severity at MM**

**Critical and potential problematic at ID**

- **What's A third-line pDDI ?**

A *third-line* pDDI was defined as a pDDI including the drug that also causes a pDDI with paracetamol.
For example: **simvastatin-warfarin**
This 3rd line pDDI may influence the pDDI between paracetamol and warfarin.

- **What's third-line drugs ?**

A third-line drug was defined as the drug that had a pDDI with the same drug that was identified to have a pDDI with paracetamol.
For example:
Simvastatin is the third-line

# Results

104 patients were admitted during the study period. 91 (87.5%) of these (mean age 86 years) were treated with paracetamol. 10% were evaluated as being at risk of potential drug-drug interactions with paracetamol. Seven of the potential drug-drug interactions were related to treatments with warfarin, one with valsartan and one with phenytoin. Nine patients were at the risk, six did experience either abnormal biochemical values or potential related clinical incidents. Four patients experienced increased INR (range 3.2–4.6), of which one patient suffered from anaemia and one with hematemesis. Two patients experienced increased ALAT/ASAT (55/42 U/l and 87/51 U/l, both females). One experienced hypertension.

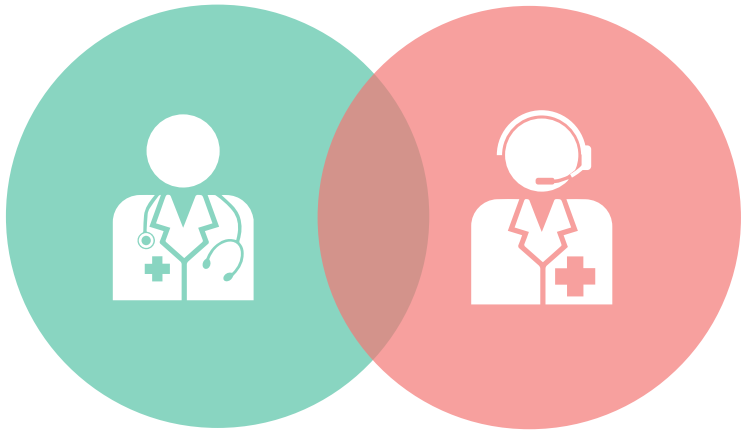
# Discussion

Furthermore, the patient's third-line drugs and
their dosage regime might be able to influence the outcome of the in- teraction between paracetamol and warfarin but to our knowledge, this is only showed in a study that investigate patients receiving warfarin and who develop an acute upper respiratory tract infection also Despite no serious outcomes like severe bleeding or death All in all, explanations not necessarily have anything to do with the general perception of an infection. And four of the investigated patients developed abnormal biochemical values or clinical incidents that could be caused by this well serious safety consideration should be given for pa- tients at risk of this interaction also This patient was also identified as malnourished, and the de- creased liver function was assessed to be associated with poor nutrition by the hospital physician. Phenytoin induces glucuronidatio and hence decreased paracetamol elimination paracetamol elimination [28]. This indicates that frailty and not age is the most important factor, The inconsistency between the applied electronic drug- drug interaction databases as seen in Table 2 is quite prominent and could be a great issue for the medication reviews performed by healthcare providers. This issue was observed in a Norwegian study as well, even though they used two other databases in their study.


Table 1: Data of the 91 patients receiving paracetamol.

| | |
|---|---|
| Gender (female/male) | 59/32 |
| | Median (range) |
| Age (years) | 86 (68–101) |
| Duration of hospitalization (days) | 8 (1–31) |
| Number of other drugs upon admission[A,B] | 7 (0–19) |
| Number of drugs at discharge[A] | 9 (2–20) |
| Number of drugs, total exposure[A] | 15 (4–29) |

[A]Not including paracetamol. [B]Eight patients did not have any registration of their medication history upon admission. The number of drugs upon admission was registered from the medication history described in the patients' journals upon the admission (not necessarily from the Department of Geriatric Medicine). The numbers of drugs at discharge and total exposure were registered from EPM and include both regular and PRN medication, and all prescriptions were registered except fluid infusions. The drugs were categorized in ATC codes. EPM = electronic patient module; PRN = as needed; pDDIs = potential drug-drug interactions; ATC = Anatomical Therapeutic Chemical Classification System.



| Patient | Duration of hospitalization (days) | On admission (g) | | Total administered | | At discharge (g) | | Maximum recommended dose complied |
|---|---|---|---|---|---|---|---|---|
| | | Regular | PRN | g | g/day[D] | Regular | PRN | |
| 1 | 7 | N/a | N/a | 28 | 4 | 2 | 2 | Yes |
| 2 | 7 | 0 | 4 | 3 | 0.43 | 0 | 4 | Yes |
| 3 | 9 | 0 | 0 | 1 | 0.11 | 0 | 0 | Yes |
| 4 | 7 | 0 | 4 | 16 | 2.29 | 3 | 0 | Yes |
| 5 | 15 | 4[A] | N/a | 50 | 3.33 | 0[C] | 0 | Yes |
| 6 | 9 | 4[A] | N/a | 36 | 4 | 4 | 0 | Yes |
| 7 | 31 | 4[A] | N/a | 91 | 2.94 | 4 | 0 | Yes |
| 8 | 7 | 0 | +[B] | 14 | 2 | 3 | 1 | Yes |
| 9 | 8 | 1[A] | N/a | 27 | 3.38 | 4 | 0 | Yes |

[A]It was not specified if the prescription was as PRN or regular medication. [B]The amount was not specified. [C]The prescription 4 × 1000 mg per day was paused the day of discharge. [D]The mean administration in grams of paracetamol per day during hospitalization. pDDI = potential drug-drug interaction; PRN = as needed; g = gram; N/a = not available.

Table 2: pDDIs described in the three different databases and the number of pDDIs for the 91 patients.

| Potential DDI with paracetamol | ID | MM | PRO | Incidents number (%) |
|---|---|---|---|---|
| Warfarin | + | + | + | 7 (7.7%) |
| Phenytoin | + | + | 0 | 1 (1.1%) |
| Valsartan | + | 0 | 0 | 1 (1.1%) |
| Isoniazid | + | ++ | 0 | 0 |
| Pneumococcal 13-valent vaccine | 0 | ++ | 0 | 0 |
| Imatinib | 0 | ++ | 0 | 0 |
| Pixantrone | 0 | ++ | 0 | 0 |
| Carbamazepine | 0 | + | 0 | 0 |
| Acenocoumarol | 0 | + | 0 | 0 |
| Lixisenatide | 0 | + | 0 | 0 |
| Zidovudine | 0 | + | 0 | 0 |
| Busulfan | 0 | + | 0 | 0 |
| Piperaquine | 0 | + | 0 | 0 |
| Diflunisal | 0 | + | 0 | 0 |
| Sulfinpyrazone | 0 | + | 0 | 0 |
| Aliskiren | + | 0 | 0 | 0 |
| Phenprocoumon | + | 0 | 0 | 0 |

0 = pDDI is not mentioned. + = pDDI is marked as "potential problematic" and "moderate severity" for ID and MM, respectively. ++ = pDDI is marked as "critical" and "major severity" for ID and MM, respectively. PM does not classify DDIs. pDDI = potential drug-drug interaction; ID = interaktionsdatabasen.dk; MM = Micromedex; PM = pro.medicin.dk.

Table 5: Information of where the patients are transferred from their clinical diagnoses: chronic and temporary diagnoses as mentioned in their medication history and patients' files.

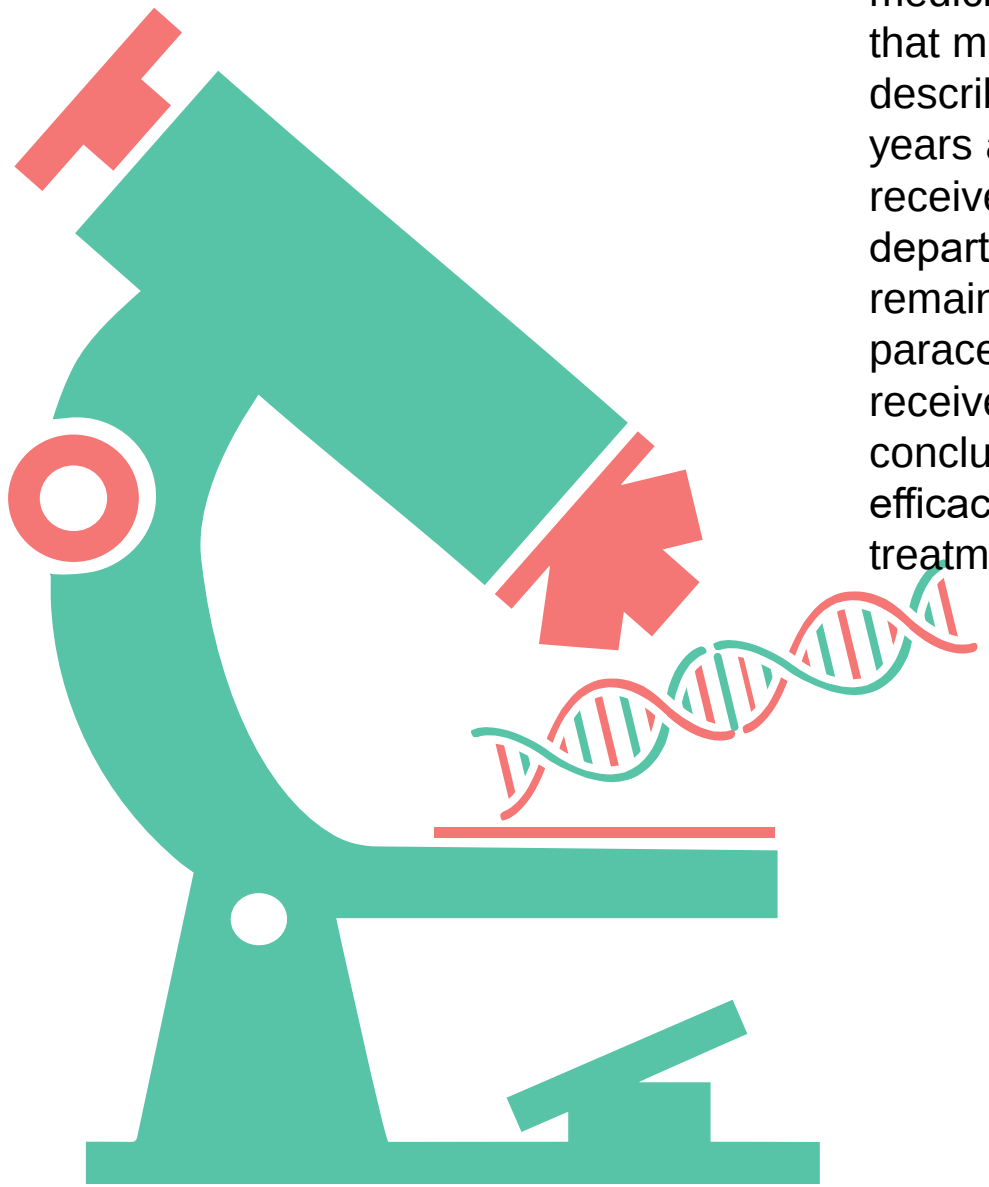
| Patient | Transferred/ admitted from | Admitted with | Chronic diagnoses | Temporary diagnoses (suspected during admission) | Incidents or altered biochemical values related to the pDDI |
|---|---|---|---|---|---|
| 1 | ED | Urinary tract infection<br>Fever | Ischemic heart disease<br>Chronic obstructive lung disease<br>Lower urinary tract symptoms<br>Atrial fibrillation<br>Herniated disc | | None |
| 2 | ED | Infection<br>Fever | Atrial fibrillation<br>Asthma<br>Depression<br>Cataract | | Increased INR and decreased haemoglobin<br>No incidents |
| 3 | ED | Fall<br>Dizziness | Type 2 diabetes<br>Atherosclerosis<br>Renal impairment<br>Hypertension<br>Atrial fibrillation | Light anaemia<br>Hypercalcemia<br>Hypotensive<br>No symptomatic urinary tract infection | Increased INR and decreased haemoglobin<br>Incident: anaemia with no bleeding |
| 4 | ED | Confusion | Ischemic heart disease<br>Cardiac insufficiency<br>Paroxysmal atrial fibrillation<br>Hypertension<br>Hypercholesterolemia<br>Angina pectoris | Insomnia<br>Hyponatraemia | Increased INR and decreased haemoglobin |
| 5 | ED | Large loss of function<br>Dehydration<br>Hyponatraemia<br>Malnutrition<br>Abdominal pains | Hypertension<br>Osteoporosis<br>Back pain related to back collapse<br>Postinfarction epilepsy | Hypotensive<br>Pain outbreaks<br>Obstipation | Increased ALAT and ASAT<br>Incidents: pain and hepatotoxicity, light ascites |
| 6 | ED | Diffuse abdominal pain<br>Urinary tract infection<br>Cysts on liver<br>Gallstones | Atrial fibrillation<br>Hypertension<br>Spinal stenosis<br>Arthrosis<br>Colostomy<br>Recurrent urinary tract infection<br>Parastomal hernia<br>Tachy-brady syndrome | Hypertensive<br>Dizziness | Increased ALAT and ASAT and INR<br>No incidents |
| 7 | ED | Dehydration<br>Emesis | Herniated disc<br>Atrial fibrillation<br>Chronic obstructive lung disease<br>Osteoporosis<br>Arthrosis<br>Diverticulosis<br>Benign kidney tumour<br>Malnutrition<br>Moderate mitral valve regurgitation | Pneumonia<br>Fall during night<br>Apnoea periods<br>Urinary tract infection<br>Delirium<br>Hallucinations<br>Hypotensive | Increased INR and decreased haemoglobin<br>Incident: hematemesis |
| 8 | Outpatient clinic | Tachycardia | Atrial fibrillation<br>Type 2 diabetes<br>Depression<br>Osteoporosis<br>Gout | Atrial flutter<br>Delirium<br>Aggressive | None |

# ED- Emergency Depar tment; pDDI potential drug-drug interaction.

Table 5: Continued.

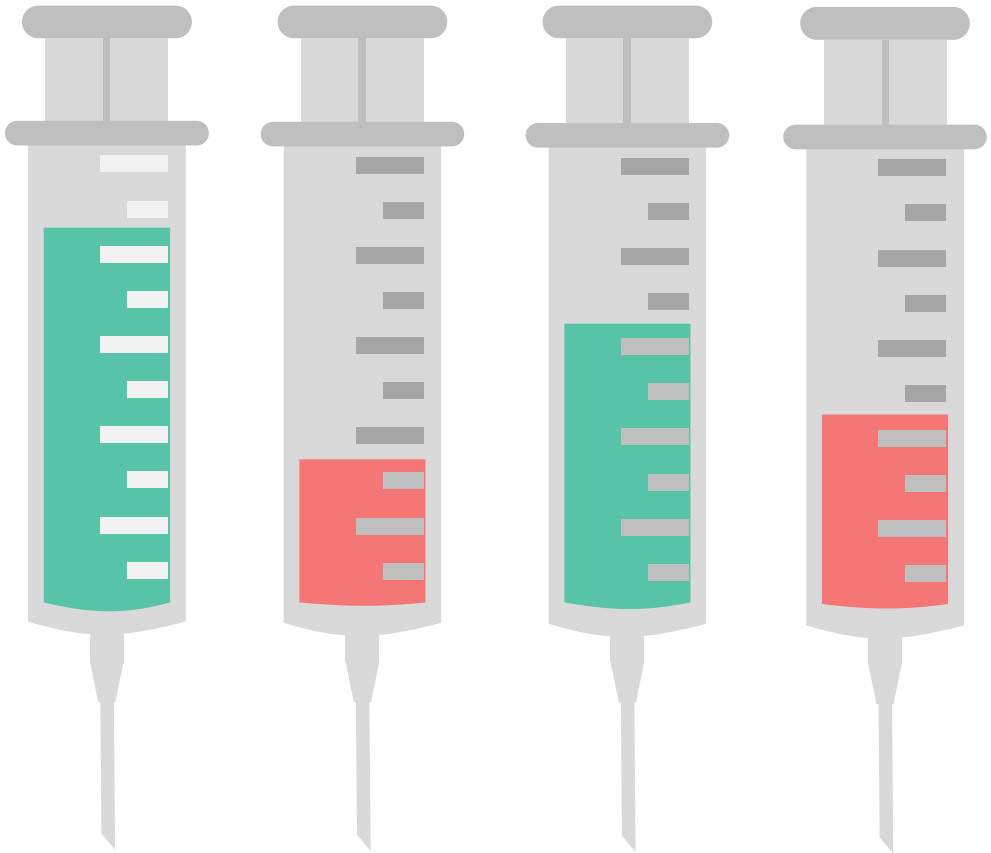
| Patient | Transferred/ admitted from | Admitted with | Chronic diagnoses | Temporary diagnoses (suspected during admission) | Incidents or altered biochemical values related to the pDDI |
|---|---|---|---|---|---|
| 9 | Outpatient clinic | General impairment | Chronic leg ulcers<br>Chronic obstructive lung disease<br>Exertional dyspnoea<br>Hypertension<br>Chronic nephropathy<br>Iron deficiency anaemia<br>Hiatal hernia<br>Peripheral oedema | Tired<br>Nausea<br>Stasis dermatitis<br>Nephrogenic anaemia<br>Dizziness | Decreased haemoglobin<br>Incident: hypertension |

ED= Emergency Department; pDDI = potential drug-drug interaction.



This study shows that most patients hospitalized at a department of geriatric medicine received treatment with paracetamol, not surprisingly, indicating that many elderly patients experience pain. A previous systematic review described that, in Denmark in 2013, 23% of patients in age group 65–79 years and 45% in age group 80–89 years
received prescribed paracetamol [27]. This indicates that patients in a department of geriatric medicine suffer from more pain than elderly in the remaining society. As several (26.4%) received more than three grams of paracetamol per day a samean, it suggests that sever elderly patients receive chronic pain treatment with paracetamol. The aforementioned review concluded that paracetamol as a chronic pain treatment showed minor efficacy and doubtful clinical relevance, suggesting that patients in chronic treatment should have their treatment reassessed

A previous study concluded that frail elderly patients had decreased liver function and decreased glucuronidation of paracetamol compared to fit elderly patients
and hence decreased paracetamol elimination
The present study showed that approximately 10% of elderly patients receiving paracetamol was at risk of pDDI shereof
The drugs found to interact with paracetamol in the Swedish study were carbamazepine, phenytoin, and phenobarbital
This is in contrast with the observations in the present study in which the interaction with warfarin was the most frequently and potentially dangerous interaction



Patients who are poor metabolizers of the CYP2C9 will also have decreased clearance . of warfarin, as the more potent S-isomer of warfarin is metabolised by this enzyme [26] and be more prone to this DDI. Due to this heterogeneity and various outcomes for patients in concomitant treatment with paracetamol and warfarin

,Phenytoin induces glucuronidation [32], as well as oxidation by inducing CYP3A4,whichmayleadtodecreasedareaunderthecurve of paracetamol, due to an enhancement of first-pass metabolism of paracetamol [33]. This can lead to decreased analgesic effect. Theoretically, the induction of CYP3A4 increases the formation of NAPQI. This canin crease the risk of hepatotoxicity due to a potential depletion of glutathione storage for further conjugation of NAPQI

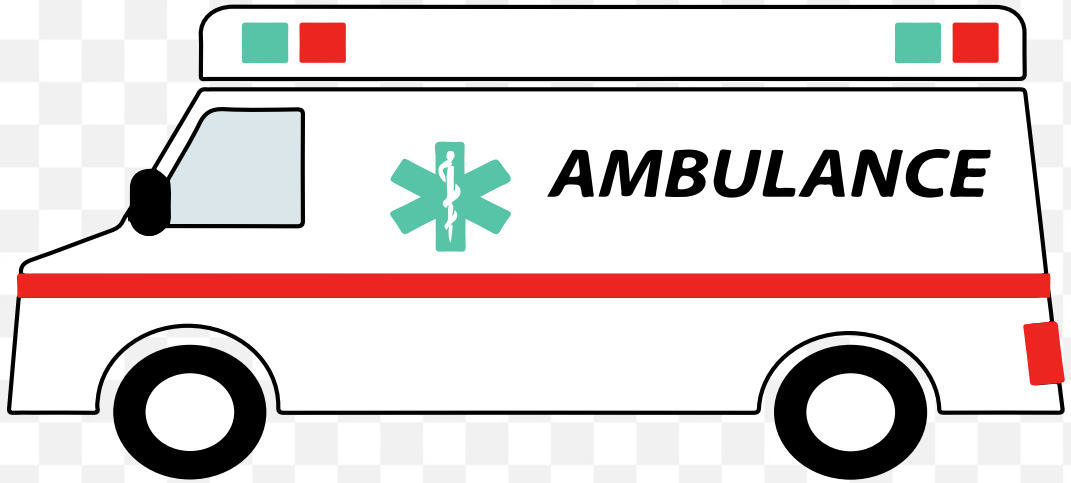
Aprevious study showed a significant increase in blood pressure in patient streated concomitantly with paracetamol and valsartan, but the mechanism of the hypertensive effect is not fully understood
the intention of this study was to show that even though paracetamol is considered the safest choice, these pDDIs are important to keep in mind both for physicians, who prescribe it, and the pharmacy, who delivers it over-the-counter to the patients. The intention is also to make the prescriber think twice when prescribing the drug, a suggestion could be to monitor the effect after a suitable time of treatment, and potentially deprescribe the well-intended treatment in case of DDI findings, other adverse effects, or lack of effect

# Conclusion

A large majority of the patients admitted to a department of geriatric medicine at a large urban secondary hospital received treatment with paracetamol. Approximately, 10% of the patients treated with paracetamol were at risk of pDDIs with paracetamol, and warfarin was the most frequent drug to act with paracetamol, imposing a risk of a serious clinical incident. None of the patients experienced any serious outcomes, suggesting that heterogeneity and confounding factors as concomitant medication, third-line pDDIs, other diseases, inflammation, metabolism, and malnutrition can contribute to the outcome. Six patients were assessed to experience either influence of biochemical values or incidents during hospitalization that could be related to the identified pDDIs.

# References

Vermehren, C. (2017) The Risk of Drug-Drug Interactions with Paracetamol in a Population of Hospitalized Geriatric Patients. *Hindawi*. [Online] 2020, 9. Available from: https://www.hindawi.com/journals/jphar/2020/1354209/.




# Thank You