Winter 1-4-2020

Evaluation of Antimicrobial Agents with Potential to Develop Adverse Mental Health in Geriatrics

Sonal M. Sekhar Dr

EVALUATION OF ANTIMICROBIAL AGENTS WITH POTENTIAL TO DEVELOP ADVERSE MENTAL HEALTH IN GERIATRICS

A Project Report Submitted to
MANIPAL ACADEMY OF HIGHER EDUCATION
In partial fulfillment for the degree of Doctor of Pharmacy
(Pharm D)

MANIPAL
ACADEMY *of* HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Submitted By:

Ms. Vaishali V. Shinde
Reg. No: 180615005

Mr. Levine M. Wilson
Reg. No: 150614013

II Pharm D (PB) and V Pharm D
Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
Manipal Academy of Higher Education,
Manipal, Karnataka, India

APRIL 2020
Under the Guidance of:

Guide:

Dr. Sonal Sekhar M, M. Pharm, Ph.D
Assistant Professor - Selection Grade
Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
Manipal, Karnataka, India.

Co-Guide:

Dr. Kavitha Saravu, MD, DNB, DTM&H
Professor & Head,
Department of Infectious Diseases,
Kasturba Medical College and Hospital,
Manipal, Karnataka, India.

MANIPAL COLLEGE
OF PHARMACEUTICAL SCIENCES
MANIPAL
(A constituent unit of MAHE, Manipal)

Certificate

This is to certify that the project report entitled "**Evaluation of Antimicrobial Agents with Potential to Develop Adverse Mental Health in Geriatrics"** by **Ms. Vaishali V. Shinde** and **Mr. Levine M. Wilson** for the completion of II PharmD (PB) and V Pharm D comprises of the bonafide work done by them in the Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and Kasturba Hospital, Manipal, under the guidance of Dr. Sonal Sekhar M, Assistant Professor-Selection Grade, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal and co-guidance of Dr. Kavitha Saravu , Professor & Head, Department of Infectious Diseases, Kasturba Medical College and Hospital, Manipal, India.

I recommend this piece of work for acceptance for the partial fulfilment of the completion of the II Pharm.D (PB) and V Pharm D program of Manipal Academy of Higher Education, Manipal for the academic year 2019-2020

Place: Manipal
Date:

Dr. Sonal Sekhar M, M. Pharm, PhD
Assistant Professor - Selection Grade
Department of Pharmacy Practice
Manipal College of Pharmaceutical Sciences
Manipal Academy of Higher Education
Manipal, Karnataka, India.

MANIPAL COLLEGE
OF PHARMACEUTICAL SCIENCES
MANIPAL
(A constituent unit of MAHE, Manipal)

Certificate

This is to certify that the project report entitled "**Evaluation of Antimicrobial Agents with Potential to Develop Adverse Mental Health in Geriatrics"** by **Ms. Vaishali V. Shinde** and **Mr. Levine M. Wilson** for the completion of II PharmD (PB) and V Pharm D comprises of the bonafide work done by them in the Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and Kasturba Hospital, Manipal, under the guidance of Dr. Sonal Sekhar M, Assistant Professor-Selection Grade, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal and co-guidance of Dr. Kavitha Saravu , Professor & Head, Department of Infectious Diseases, Kasturba Medical College and Hospital, Manipal, India.

I recommend this piece of work for acceptance for the partial fulfilment of the completion of the II Pharm.D (PB) and V Pharm D program of Manipal Academy of Higher Education, Manipal for the academic year 2019-2020

Place: Manipal
Date:

Dr. Kavitha Saravu, MD, DNB, DTM&H
Professor & Head,
Department of Infectious Diseases,
Kasturba Medical College and Hospital,
Manipal, Karnataka, India.

MANIPAL COLLEGE
OF PHARMACEUTICAL SCIENCES
MANIPAL
(A constituent unit of MAHE, Manipal)

Certificate

This is to certify that the project report entitled "**Evaluation of Antimicrobial Agents with Potential to Develop Adverse Mental Health in Geriatrics"** by **Ms. Vaishali V. Shinde** and **Mr. Levine M. Wilson** for the completion of II PharmD (PB) and V Pharm D comprises of the bonafide work done by them in the Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and Kasturba Hospital, Manipal, under the guidance of Dr. Sonal Sekhar M, Assistant Professor-Selection Grade, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal and co-guidance of Dr. Kavitha Saravu , Professor & Head, Department of Infectious Diseases, Kasturba Medical College and Hospital, Manipal, India.

I recommend this piece of work for acceptance for the partial fulfilment of the completion of the II Pharm.D (PB) and V Pharm D program of Manipal Academy of Higher Education, Manipal for the academic year 2019-2020

Place: Manipal
Date:

Dr. Mahadev Rao, **M. Pharm, PhD**
Professor and Head
Department of Pharmacy Practice
Manipal College of Pharmaceutical Sciences
Manipal Academy of Higher Education
Manipal, Karnataka, India.

MANIPAL COLLEGE
OF PHARMACEUTICAL SCIENCES
MANIPAL
(A constituent unit of MAHE, Manipal)

Certificate

This is to certify that the project report entitled "**Evaluation of Antimicrobial Agents with Potential to Develop Adverse Mental Health in Geriatrics"** by **Ms. Vaishali V. Shinde** and **Mr. Levine M. Wilson** for the completion of II PharmD (PB) and V Pharm D comprises of the bonafide work done by them in the Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and Kasturba Hospital, Manipal, under the guidance of Dr. Sonal Sekhar M, Assistant Professor-Selection Grade, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal and co-guidance of Dr. Kavitha Saravu , Professor & Head, Department of Infectious Diseases, Kasturba Medical College and Hospital, Manipal, India.

I recommend this piece of work for acceptance for the partial fulfilment of the completion of the II Pharm.D (PB) and V Pharm D program of Manipal Academy of Higher Education, Manipal for the academic year 2019-2020

Place: Manipal
Date:

Dr. C. Mallikarjuna Rao, M.Pharm, PhD
Principal & Professor,
Manipal College of Pharmaceutical Sciences
Manipal Academy of Higher Education
Manipal, Karnataka, India - 576104.

MANIPAL COLLEGE
OF PHARMACEUTICAL SCIENCES
MANIPAL
(A constituent unit of MAHE, Manipal)

Declaration

We hereby declare that the project entitled **"Evaluation of Antimicrobial Agents with Potential to Develop Adverse Mental Health in Geriatrics"** was carried out under the guidance of **Dr. Sonal Sekhar M,** Assistant Professor - Selection Grade, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences and co-guidance of **Dr. Kavitha Saravu,** Professor & Head, Department of Infectious Diseases, Kasturba Medical College and Hospital, Manipal Academy of Higher Education, Manipal, India. The extent and source of information derived from the existing literature have been indicated throughout the project work at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree purpose for this or any other university.

Place: Manipal

Date:

Ms. Vaishali V. Shinde
(Reg. No. 180615005)

Mr. Levine M. Wilson
(Reg. No: 150614013)

ACKNOWLEDGEMENTS

At the outset, we express our utmost gratefulness to the almighty for the blessing throughout this study.

We are extremely thankful to our parents for giving us the opportunity to pursue our dreams and for their unconditional love, care, concern and support throughout our life.

We humbly owe our gratitude and sincere regards to our respected teacher and guide, ***Dr. Sonal Sekhar M,. Assistant Professor-Selection Grade****, Dept. of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal, for his valuable guidance, encouragement, untiring patience and support during all the stages of our work. His encouragement and fruitful suggestions have enabled to make our work worthy of presentation.*

Our heartfelt thanks to ***Dr. Mahadev Rao,*** *our Professor and Head, for his encouragement and timely consent for carrying out the study and making this project work a success.*

We extent our special thanks to our co guide, ***Dr. Kavitha Saravu, Professor and Head of Dept. of Infectious Diseases,*** *Kasturba Hospital, Manipal who has been instrumental in the timely completion of this work and without whom this work would not have been a success.*

We would also like to thank ***Dr. Raviraja V. Acharya****, Professor and Head of Department of Medicine and the entire Department of Medicine for their cooperation and for providing us the site for our research work.*

We thank our beloved principal, ***Dr. C. Mallikarjuna Rao****, Manipal College of Pharmaceutical Sciences, Manipal for providing us with all the facilities to move forward in our career.*

We extend our sincere and heartfelt thanks to our teachers; ***Dr. Sreedharan N, Mr. John Preshanth K****,* ***Dr. Girish Thunga, Dr. Vijayanarayana K, Mr. Prasanna K. Shetty, Dr. Surulivelrajan M, Dr. Leelavathi D. Acharya, Dr. Rajesh V, Dr. Rajesh R, Dr. Kanav Khera*** *and nonteaching staff* ***Mr. Abhilash and Mrs. Asha*** *for their endless support and cooperation.*

Our special thanks to ***Ms. Shilia Jacob Kurian****, Research Scholar, Department of Pharmacy Practice and our seniors, especially* ***Rinkal Kotadia, Rajani Singh, Priyanka Pai, Benitta Mathews and Ashley Thalody*** *who contributed for the successful completion of our study.*

My hearty thanks to our dear friends ***Rachana B, Divya M and Manya R*** *for their timely support and for all those best moments shared with them.*

Lastly, we offer our regards and blessings to all those who supported us in any aspect during the completion of our project.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
BBB	Blood Brain Barrier
CD8	Cluster of Differentiation 8
CD4	Cluster of Differentiation 4
CNS	Central Nervous System
CRF	Case Report Form
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
LRTI	Lower Respiratory Tract Infection
MAC	Mycobacterium Avium Complex
MDR	Multi Drug Resistance
PIS	Participant Information Sheet
PD	Pharmacodynamic
PK	Pharmacokinetic
RCT	Randomized Clinical Trial
RTI	Respiratory Tract Infection
STD	Sexually Transmitted Diseases
US-FDA	United States Food and Drug Administration
UTI	Urinary Tract Infection

ABSTRACT

Background: With advanced age, there is increased risk of various infections. Antimicrobial agents are majorly prescribed for management of these infections. Due to age-related physiological changes, many of the antimicrobial agents cause adverse mental health. Therefore, we evaluated the geriatric antimicrobial prescription to determine its potential to cause mental health issue.

Objectives:

- To prepare a checklist for antimicrobials which have the potential to cause adverse mental health.
- Evaluate the geriatric antimicrobial prescription to determine its potential to cause mental health issue.
- To determine antimicrobial-related mental health problems in geriatric patients.

Methods: A prospective observational study was conducted in all the medicine departments of Kasturba Hospital (KH), Manipal. The geriatric patients prescribed with antimicrobial agents were recruited based on the inclusion and exclusion criteria. A checklist of antimicrobial agents with potential to develop adverse mental health was prepared by performing thorough literature review and hospital formulary of KH, Manipal. All the relevant data was collected in the case report form and the potential agents that could cause adverse mental health were identified using the checklist. The data was entered in IBM SPSS version 25.0 and suitable descriptive statistical analysis was carried out.

Results: Out of the 115 geriatric patients, 89 (77.4%) were prescribed with a total of 178 antimicrobial agents with potential to develop adverse mental health. Average number of antimicrobials per prescription, which has the potential to cause mental health adverse effect is 1.5. These prescriptions comprised of 21 drugs from various classes of antimicrobial agents listed in the checklist prepared. Out of the 89 patients who received the antimicrobials with potential to cause the adverse mental health, 10 patients developed the adverse drug reactions such as insomnia, agitation, delirium, anxiety, nightmares, and seizures. Female geriatric patients have 3.5 times higher risk for developing the adverse mental health problems compared to male patients after the antimicrobial use (OR: 3.5; 95% CI:0.06-1.41). However, the risk for development of adverse mental health problems in patients with renal dysfunction are 28% times less likely than the patients with normal renal function (OR: 0.28; 95% CI:0.08-6.15).

Conclusions:

The major antimicrobial classes, which have adverse mental health issues in geriatrics are beta-lactams, tetracyclines, cephalosporins, fluoroquinolones, macrolides, sulfonamides, aminoglycosides, carbapenems, oxazolidines, other antibiotics, antifungals, antimalarial and antivirals. Risk estimation shows that women geriatric patients have higher risk for developing the adverse mental health problems compared to men after the antimicrobial use. However, unlike other studies renal dysfunction was not found to be a risk factor for developing the adverse mental health. Potential mechanism of toxicity differs among the agents and the etiology also remains unidentified in some cases. However, the incidences may be increased due to presence of co-morbidities, drug interaction and age-related changes.

INTRODUCTION

1. INTRODUCTION

1.1 Increased Risk of Infection in Geriatrics

In majority of individuals aged 65 years and older, the primary cause of death is infection. Infection may be caused due to compromised immunity. There are a few age-related physiological changes which lead to infections in geriatrics:

- Due to alterations in barriers posed by gastrointestinal tract, lungs, and skin (and other mucosal linings). There can be increased risk of pathogenic organisms' invasion.
- Due to change in humoral and cellular immunity, decreased specific cell population, decreased production of specific cytokines (e.g., Interleukin-2) and loss of proliferative capacity of immune cells, there can be an increased risk of intracellular pathogens.
- Due to impaired signal transduction after cytokine binding, there are chances of impaired defense against fungal and viral pathogens.
- Reduction in receptors and cells like CD8 and CD4. There can be decrease in the antibody response to vaccines.
- Due to reduction in naïve B cells, there can be impairment in immunoglobulin production and specificity of antibody responses.

There is a greater impairment in immunity, which results in increased risk of infections and poorer vaccine responses in geriatrics along with chronic diseases like, diabetes, chronic obstructive pulmonary disease, or heart failure.

Geriatric patients living in communal residence such as daycare center or senior centers, have a greater risk of infection.

1.2 Presentation of Disease in Geriatrics

It is difficult to identify infection in geriatrics, since the signs and symptoms in geriatrics can be different to that of the typical signs and symptoms in younger adults. For example, in case of infection, there may be lack of fever or localization, or specific infection signs and symptoms. Similarly, in case of pneumonia, instead of fever, productive cough, chest pain, the signs and symptoms seen can be low-grade fever and increased oxygen demand.

In geriatrics, the infections may be identified due to symptoms such as confusion, falling and anorexia. But these symptoms are useful only for provisional diagnosis and based on that

empiric treatment can be initiated after careful physical examination, medical review and other diagnostic tests. However, once the diagnostic test results are negative, the empiric treatment should be discontinued.

1.3 Antimicrobial Therapy

Antimicrobials are considered for management of infections, which are serious and life-threatening, for example, sepsis, pneumonia, influenza, etc. Antimicrobial therapy in geriatrics is determined by age-related pharmacokinetic (PK) changes and increased risk of exposure to multi-drug resistant (MDR) organisms.

1.3.1 Choice of antimicrobial agent:

The choice of initial antimicrobial is same as in younger adults for most infections. However, precautions must be taken when initiating broader empiric treatment in geriatrics as there is an increased risk of infection with drug-resistant organisms. This can be because of recent hospitalization, dialysis, recent antimicrobial treatment, indwelling devices or due to residence in community center.

Seriously ill geriatric patients with conditions like pneumonia, sepsis or other life-threatening infections are suspected, the broader initial coverage of antimicrobial may be appropriate. However, it is important to narrow down the antimicrobial regimen when the cultures are available to decrease the risk of antimicrobial resistance in the patient. It is also important to consider the interactions of antimicrobial drugs and other drugs in geriatrics, especially the drugs with narrow therapeutic index. Example, commonly seen interactions are for antimicrobials with warfarin, digoxin, antacids, and H_2-receptor antagonists. However, the interaction is difficult to predict for some antimicrobials.

1.3.2 Dosing:

Dosing is very critical in geriatrics, as the PK parameters change in them due to age and co-morbidities. For the antimicrobials to show its action, it is important to maintain the drug levels in therapeutic range, thus, appropriate dosing is required. [(1)]

- **Absorption**: Due to increasing age, there can be changes in gastrointestinal tract, such as, delayed gastric emptying, reduced splanchnic blood flow and alterations in pH. This can affect the bioavailability of the drugs.

- **Distribution**: The distribution can be affected due to increased adipose tissues in geriatrics. This can lead to increased distribution of lipophilic drugs (For examples, fluoroquinolone, macrolides, tetracyclines, antifungals, etc.) in tissue compartment, which leads to increased half-life of lipid soluble drugs. Decrease in total body water and lean mass decreases the solubility of water-soluble drugs in tissue compartment. This means there an increase in the plasma concentration of water-soluble drugs, such as, aminoglycosides, beta-lactams, etc. In such situation, loading dose of water-soluble drugs is required when indicated in case of serious infections. Decrease in plasma albumin due to various reasons can also increase the concentration of free drug in plasma, for example, penicillin, ceftriaxone, sulfonamides, and clindamycin.

- **Metabolism**: Due to reduced hepatic blood flow or reduced hepatic function, as a result of ageing or liver disease, the metabolism of hepatically metabolized antimicrobials will be affected. It may increase the half-life of such drugs such as macrolides, fluoroquinolones, azole antifungals, etc.

- **Elimination**: With increasing age, there is reduction in function of lungs, kidneys, bladder, gastrointestinal tract, and circulatory system, which affects the elimination of drug from the body. Thus, may lead to accumulation of drug in the body and cause toxicity. Kidneys are essential for elimination of antimicrobials such as beta-lactams, aminoglycosides, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole, etc. [(2)]

1.4 Mental Health in Geriatrics

Geriatric patients have major risk factors for drug-induced adverse mental health, which can include advanced age, polypharmacy, underlying neurologic disorders, kidney impairment and other co-morbidities. The adverse mental health effects can be observed in geriatrics due to alterations in neurotransmission and signal transduction, changes in PK and pharmacodynamics (PD) changes and polypharmacy. Additionally, uremia can cause increase in blood-brain barrier (BBB) penetration and decrease in albumin can cause increase in free fraction of drugs. Certain co-morbidities, such as respiratory failure, heart failure or myocardial infarction, can lead to change in oxygen and nutrient delivery to central nervous system (CNS), may predispose to delirium. [(3)]

1.5 Antimicrobial-Induced Adverse Mental Health in Geriatrics

1.5.1 Antibiotics

1.5.1.1 Penicillin

Among the penicillin agents, piperacillin and tazobactam are reported to have the most neurotoxicity. Most cases are reported in patients with advanced renal insufficiency (creatinine clearance <15 mL/min). Patients experience neurotoxic events such as seizures, convulsions, hallucinations, confusion, disorientation, delirium, insomnia, and bizarre behavior. The onset of symptoms is usually within 7 days of therapy initiation. There are several predisposing conditions, such as advancing age, hypoalbuminemia, malnutrition, and inflammation. These increase the risk of piperacillin and tazobactam accumulation in patients with renal dysfunction. [(4)] Ampicillin have been reported to show adverse mental events like convulsions, seizures, hallucinations, and mania. While amoxicillin is associated with agitation, anxiety, confusion, insomnia, seizures, unusual behavior.

1.5.1.2 Tetracycline

Tetracycline agents are usually prescribed for atypical pneumonias, uncomplicated skin and soft tissue infections, etc. Neurotoxicity is limited in this class. Doxycycline-induced insomnia is commonly observed adverse mental health. [(4)]

1.5.1.3 Cephalosporin

Cephalosporins show various adverse mental health effects within all four generations. The most frequent reports are seen in cefepime, ceftazidime, cefuroxime, and cefazolin. Commonly observed adverse drug reactions (ADRs) for cefazolin and ceftazidime are encephalopathy and seizures. Cephalexin and cefuroxime can cause seizures. While cefepime can cause confusion, hallucinations, agitation, convulsion, and delirium. [(4)]

Renal impairment and excess dosage have increased risk of neurotoxicity with use of cephalosporins, but it is also reported in patients with normal creatinine clearance. Typically, the ADRs are seen within 10 days of initiation of regimen and resolve within 7 days after discontinuation of the medication. [(5)]

1.5.1.4 Fluoroquinolones

Fluoroquinolones are used as broad-spectrum antimicrobial agents in treatment of infectious diseases. Since 2008, United States Food and Drug Administration (US FDA) mandated black box warnings and package inserts which have been revised over the years. One of the warnings include mental health side effects which are listed under CNS effects in the warnings and precautions section of the drug label and is differed by individual drug. Owing to this, FDA has advised to restrict the use of fluoroquinolones for some uncomplicated infections. [6]

Ciprofloxacin and moxifloxacin have seen to cause psychosis, delirium, agitation, depression, hallucinations, nightmares, and seizures. While levofloxacin was found to cause insomnia, psychosis, delirium, agitation, depression, hallucinations, nightmares, and seizures. Norfloxacin was reported to cause seizures, psychosis, and confusion.

1.5.1.5 Macrolides

Macrolides such as azithromycin, clarithromycin and erythromycin have been extensively used in treatment of various infectious diseases such as sexually transmitted diseases (STDs), respiratory tract infections (RTIs), peptic ulcers due to *Helicobacter pylori* and *Mycobacterium avium* complex (MAC) infection. More commonly associated drug with neurotoxicity is clarithromycin, however, azithromycin has been associated to cause delirium and erythromycin to cause seizures. Anxiety, confusion, insomnia, psychosis, convulsions, disorientation, hallucinations, mania, and seizures are associated with clarithromycin. [3,4]

1.5.1.6 Sulfonamides

Sulfonamides such as sulfasalazine and the combination of trimethoprim and sulfamethoxazole provide bactericidal effect against many infectious diseases. These include the infections caused by gram-positive and gram-negative bacilli, such as skin and soft tissue infections, RTIs and urinary tract infection (UTI). Trimethoprim and Sulfamethoxazole are also used to prevent many opportunistic infections in immune compromised diseases like human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). The most seen mental adverse effects of this combination include psychosis, agitation, seizures, hallucinations, depression, and nervousness. While sulfasalazine is reported to cause encephalopathy and seizures.

1.5.1.7 Aminoglycosides

Aminoglycosides are mostly used in management of gram-negative infections. Gentamicin and Tobramycin have been associated with psychosis, encephalopathy, seizure, delirium, confusion and disorientation, while kanamycin with nervousness and restlessness and neomycin with convulsions. [4]

1.5.1.8 Carbapenems

Carbapenems are primarily associated with seizures and seizure-like activity. This is also mentioned in the FDA label. Imipenem-cilastatin was reported to cause seizures in elderly. The incidence rate was 1.5% - 2% as per the post-marketing reports. Meropenem caused seizures, delirium, and hallucinations. Ertapenem caused seizures, hallucinations, confusion, disorientation, somnolence, aggression, delirium, and encephalopathy. [4,7]

1.5.1.9 Oxazolidinone

Post-marketing reports indicate growing trend of adverse mental health with linezolid such as encephalopathy, seizure, and delirium.

1.5.1.10 Other Antibiotics

Several case reports outline that metronidazole caused encephalopathy, confusion, disorientation, insomnia, seizure, and depression. Polymyxin caused confusion, hallucinations, and seizures. Nitrofurantoin caused depression and confusion. A prospective cohort study reported that advanced age was associated with isoniazid-induced adverse effects which included encephalopathy, memory impairment, psychosis, and seizures. [4] Rifampin caused confusion, somnolence, difficulty in concentration, psychotic disorder, and unusual change in behaviour. Ethambutol caused hallucinations and mania.

1.5.2 Antifungal

Antifungal amphotericin B has been associated with dementia, confusion, and disorientation.[3] The azole group of antifungals like fluconazole have been reported to cause seizures, while ketoconazole has been associated with disorientation and somnolence.

1.5.3 Antimalarial

Mefloquine has been reported to induce confusion, encephalopathy, insomnia, memory impairment, seizure, somnolence, aggressive behaviour, agitation, anxiety, risk for suicide, delirium, delusional disorder, depression, hallucinations, mania, mood swings, nightmares, panic attack, phobia and psychotic disorder. Quinine has been reported to cause confusion and restlessness. Primaquine has been associated with depression and psychotic disorder, while chloroquine associated with seizures. [(3)]

1.5.4 Antiviral

Ganciclovir-induced encephalopathy and seizures have been observed in some case reports. Acyclovir has been associated with confusion, dizziness, encephalopathy, seizure and somnolence. [(3)]

1.6 Need for the study

With increase in the standard of medical care, there has been an increase in life expectancy of human beings, leading to an increase in the geriatric population. The geriatric population is at an increased risk of experiencing ADRs due to alterations in PK properties. This leads to distortion in drug absorption, distribution, metabolism, elimination, and protein binding, which increase the risk of ADR. With increase in age, the muscle mass decreases, and the body fat can double, altering the PK changes of lipophilic drugs. They are also at an increased risk of drug-induced adverse mental health issues due to alterations in neurotransmission and signal transduction, changes in PK /PD, and increased medication burden.

Therefore, it is important that the geriatric prescription guidelines are to be followed strictly to avoid the ADRs in geriatrics. Besides, majority of the studies conducted on safety of antimicrobials on mental health in geriatrics were from Western population. Extrapolating that data on Indian population may not be justified. Hence, we designed this study to evaluate the use of antimicrobial drugs in geriatrics as per geriatric prescription guidelines and assess if these drugs have any potential to develop adverse mental health in geriatric population.

AIMS & OBJECTIVES

2.1 AIM:

To study the antimicrobial agents' usage in geriatric patients and mental health problems related to these agents.

2.2 OBJECTIVES:

- To prepare a checklist of drugs as per the hospital formulary, which have the potential to cause adverse mental health.
- Evaluate the geriatric antimicrobial prescription to determine its potential to cause mental health issue.
- To identify antimicrobial-related mental health problems in geriatric patients

METHODOLOGY

3. METHODOLOGY

3.1 Study Site: The study was conducted in all medicine units of Kasturba Medical College Hospital, Manipal, a tertiary care hospital in South-India.

3.2 Study Design: Cross-sectional study.

3.3 Study Period: 8 months (August 2019 – March 2020)

3.4 Sample Size: 115 geriatric patients prescribed with antimicrobial agents during the study period and admitted in the Medicine units of Kasturba Medical College Hospital, Manipal.

3.5 Ethical Approval: The protocol for this study was approved by the Institutional Ethical Committee of Kasturba Medical College and Kasturba Hospital, Manipal. (IEC - 588/2019) [Appendix I]. Clinical Trial Registry-India (CTRI) registration was taken (registration number CTRI/2019/09/021420).

3.6 Study Criteria:

3.6.1 Inclusion:

- Geriatric patients (65 years and above)
- Patients of both gender
- Patients receiving antimicrobial drugs

3.6.2 Exclusion:

- Geriatric patients who have not been prescribed antimicrobial drugs
- Other than geriatric population
- Patients who have psychiatric disorder or on anti-psychotic drugs

3.7 Data Source:

The study population broadly represents the South-Indian population. All relevant data was obtained from the medical records of geriatric patients prescribed with antimicrobial agents during the study period.

3.8 Study Material:

- Participant Information Sheet (PIS) - Used to provide necessary details (purpose, benefits/risks, procedure) regarding the study [Appendix II a, b].
- Informed Consent Form (ICF)– An Informed consent form in Kannada or English was obtained from each participant/ Legally Authorized Representative before study initiation [Appendix III a, b].
- Case Report Form (CRF) - To collect patient data (demographics, past medical history, diagnosis, treatment regimen, lab data & other clinical investigations) [Appendix IV].

3.9 Operation Modality:

The study was carried out in the following steps:

Step 1: Preparing the checklist for the antimicrobial agents

Step 2: Designing the data collection form or case report form

Step 3: Data collection

Step 4: Data entry

Step 5: Evaluation and analysis

Step 1: Preparing the checklist for list of antimicrobial agents

A checklist of antimicrobial agents was prepared to list down all the potential drugs that cause adverse mental health in geriatrics. A thorough literature review was done on antimicrobial agents causing adverse mental health in geriatrics. Only four main categories of antimicrobial drugs were included, namely, antibiotics, other antibiotics (anaerobic agents, anti-mycobacterial), antifungals and antivirals (expect anti-HIV agents). An inclusion criterion was made based on the antimicrobials available in the Kasturba Hospital's hospital formulary.

Step 2: Designing the data collection form or case report form

As per the requirement of study protocol, a data collection form was made to include all the relevant data. Date such as the patient demographics, past medical history, medication history, co-morbidities, previous exposure to antimicrobials, diagnosis, lab data, treatment regimen, adverse effects seen and other relevant clinical data.

Step 3: Data collection

Geriatric patients (65 years and above) of both genders were prospectively identified in all the medicine departments of Kasturba Medical College Hospital, who were prescribed with anti-microbial agents. Based on the inclusion and exclusion criteria, participants were recruited after they or their legal representatives (in unconscious patients) have been explained about the study in detail via using a participation Information sheet and then obtaining their informed consent. All the relevant data from patient's medical record was collected in the case report form.

Step 4: Data entry

The data was entered in statistical package for the social sciences (SPSS) version 25.0 for the data analysis.

Step 5: Evaluation and analysis:

Suitable descriptive statistical analysis was carried. Nominal data were expressed as frequency and percentage and continuous variables using descriptive statistics (Mean ± Standard Deviation).

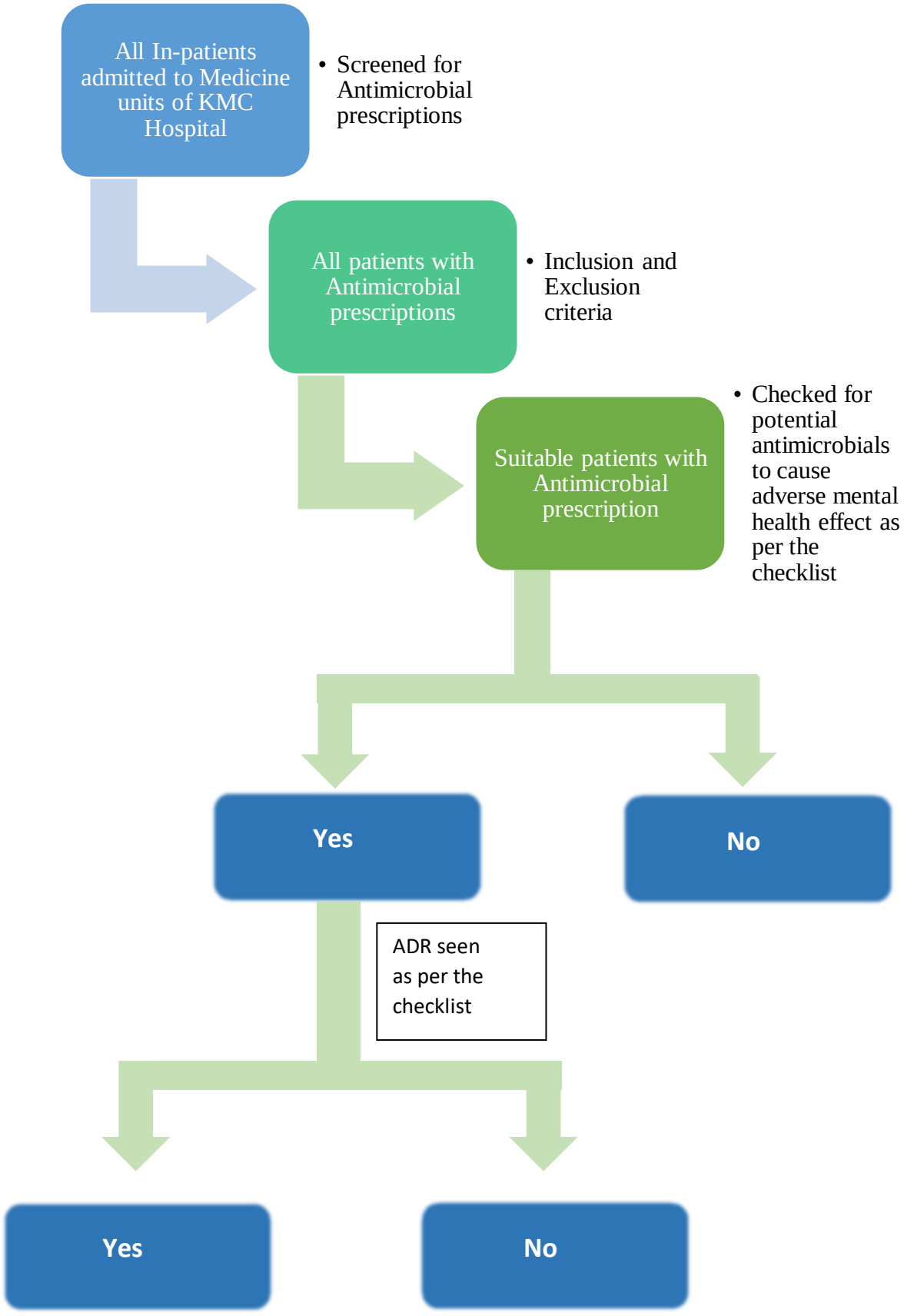

Figure 1: Study Flow Chart

RESULTS

4. RESULTS

4.1 Developed Checklist of Antimicrobial Agents with Potential Adverse Mental Health

A checklist was prepared which consisting of antimicrobial agents that have potential to develop adverse mental health [Table 1]. The checklist was developed by thorough literature review using key words "adverse mental health", "antimicrobials", "antibiotics", etc. and by referring hospital formulary of Kasturba Hospital, Manipal.

Table 1: Checklist of Antimicrobials with Potential to Cause Adverse Mental Health

Sl. No.	Drugs	Adverse Mental Health
I	**Antibiotics**	
1)	**Penicillin**	
a	Ampicillin	Convulsions, Hallucinations, Mania, Seizures
b	Piperacillin/ tazobactam	Behavior Bizarre, Confusion, Convulsions, Delirium, Disorientation, Hallucinations, Insomnia, Seizures
c	Amoxicillin	Agitation, Anxiety, Confusion, Insomnia, Seizures, Unusual Behavior
2)	**Tetracycline-**	
a	Doxycycline	Insomnia, Suicidal Thoughts
b	Minocycline	Depersonalization, Somnolence
3)	**Cephalosporin**	
a	Cefazolin	Encephalopathy, Seizures
b	Cephalexin	Seizures
c	Ceftazidime	Encephalopathy, Seizures
d	Cefepime	Agitation, Confusion, Convulsion, Delirium, Hallucinations
e	Cefuroxime	Seizures
4)	**Fluoroquinolones**	
a	Ciprofloxacin	Agitation, Delirium, Depression, Hallucinations, Nightmares, Psychosis, Seizures
b	Levofloxacin	Agitation, Delirium, Depression, Hallucinations, Insomnia, Nightmares, Psychosis, Seizures
c	Moxifloxacin	Agitation, Delirium, Depression, Hallucinations, Nightmares, Psychosis, Seizures
d	Norfloxacin	Confusion, Psychosis, Seizures
5)	**Macrolide**	
a	Azithromycin	Delirium

b	Clarithromycin	Anxiety, Confusion, Convulsions, Disorientation, Hallucinations, Insomnia, Mania, Psychosis, Seizures
c	Erythromycin	Seizures
6)	**Sulfonamides**	
a	Sulfamethoxazole-Trimethoprim	Agitation, Depression, Hallucinations, Nervousness, Psychosis, Seizures
b	Sulfasalazine	Encephalopathy, Seizures
7)	**Aminoglycosides**	
a	Gentamicin	Delirium, Encephalopathy, Psychosis, Seizure
b	Tobramycin	Confusion, Delirium, Disorientation, Psychosis
c	Kanamycin	Nervousness, Restlessness
d	Neomycin	Convulsions
8)	**Carbapenems**	
a	Imipenem-Cilastatin	Seizures
b	Meropenem	Delirium, Hallucinations, Seizures
c	Ertapenem	Aggression, Confusion, Delirium, Disorientation, Encephalopathy, Hallucinations, Seizures, Somnolence
9)	**Oxazolidinone**	
a	Linezolid	Delirium, Encephalopathy, Seizure
II	**Other antibiotics**	
a	Metronidazole	Confusion, Depression, Disorientation, Encephalopathy, Insomnia, Seizure
b	Polymyxin	Confusion, Hallucinations, Seizures
c	Nitrofurantoin	Confusion, Depression
d	Isoniazid	Disturbance, Encephalopathy, Hallucinations, , Lethargy, Memory Impairment, Paranoia, Psychosis, Seizures, Sleep
e	Rifampin	Confusion, Psychotic Disorder, Somnolence, Unable to concentrate, Unusual change in behaviour
f	Ethambutol	Hallucinations, Mania
III	**Antifungal**	
a	Amphotericin B	Confusion, Dementia, Disorientation
b	Fluconazole	Insomnia, Seizure, Somnolence
c	Ketoconazole	Disorientation, Somnolence
IV	**Antimalarial**	
a	Quinine	Confusion, Restlessness
b	Mefloquine	Aggressive behaviour, Agitation, Anxiety, Confusion, Delirium, Delusional disorder, Depression, Encephalopathy, Hallucinations, Insomnia, Mania, Memory impairment, Mood swings, Nightmares, Panic attack, Phobia, Psychotic disorder, Risk for suicide, Seizure, Somnolence
c	Primaquine	Depression, Psychotic disorder
d	Chloroquine	Seizure

V	Antiviral	
a	Ganciclovir	Encephalopathy, Seizure
b	Acyclovir	Confusion, Dizziness, Encephalopathy, Seizure, Somnolence
c	Valganciclovir	Depression, insomnia, anxiety
d	Oseltamivir	Delirium, Delusions, Hallucinations, Nightmares, Suicidality, Confusion, Disturbance of Consciousness, Seizure, Mania, Anxiety

4.2 Demographic Details of the Geriatric Patients

A total number of 115 patients were taken from all the Medicine units of Kasturba Medical College Hospital, Manipal, during the period October 2019 to February 2020. 51 (44.3%) were males and 64 (55.7%) were females [Table 2].

Table 2: Demographic Details of the Geriatric Patients

Patient Demographics	No of patients (%) / Mean± SD
Age (Mean ± SD) **[years]**	71.90 ± 6.186
Gender: Male Female	 51 (44.3%) 64 (55.7%)
Duration of Hospitalization (Mean ± SD) **[days]**	11.82 ± 6.962
Alcoholic Yes No	 16 (13.9%) 99 (86.1%)
Smoking Yes No	 8 (7.0%) 107 (93%)
No. of Co-morbidities (Mean ± SD)	1.74 ± 1.332

4.3 Indication for Antimicrobial agents in the Patients

Out of total 115 geriatric patients, 45 (39.1%) patients received empirical antimicrobial therapy while, 70 (60.9%) received definitive therapy of antimicrobial agents.

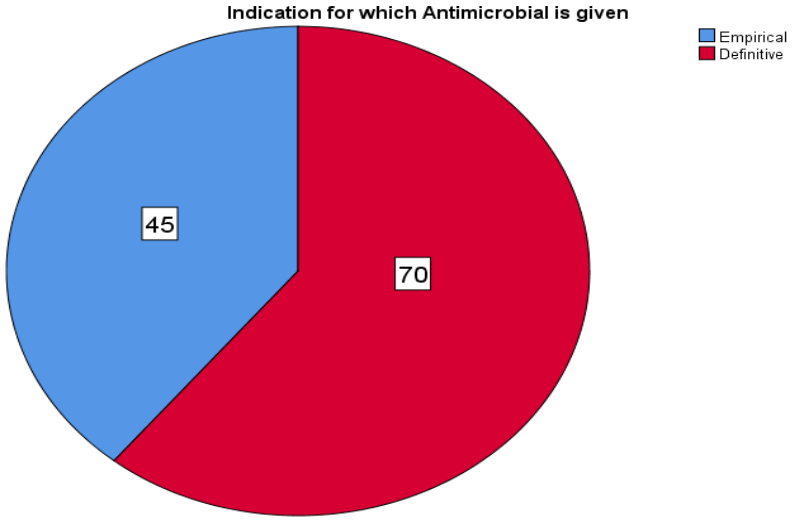

Figure 2: Indication for Antimicrobial Agents in the patients

4.4 Conditions for Antimicrobial Agent Prescription in Geriatric Patients

Out of 115 patients who received different antimicrobials, 25 (21.73%) were have pneumonia, 21(18.26%) were have lower respiratory tract infections (LRTI) and 11 (9.56%) were have UTI [Table 3].

Table 3: Conditions for Antimicrobial Prescribed in Geriatric Patients

Conditions	No. of Patients (%)
Pneumonia	25 (21.73%)
LRTI	21 (18.26%)
UTI	11 (9.56%)
Urosepsis	9 (7.82%)
Suspected infections	13 (11.3%)
Others	36 (31.3%)

4.5 Combination of Antimicrobial agents prescribed in the Patients

The geriatric patients were prescribed antimicrobial agents either as monotherapy (39; 33.9%) or as combination (76; 66.1%) [Table 4]. Total 265 drugs were prescribed to 115 patients.

Table 4: Combination of Antimicrobial Agents prescribed

No. of drugs in combination of Antimicrobials	No. of Patients (%)
Two antimicrobial agents	34 (29.6%)
Three antimicrobial agents	25 (21.7%)
Four antimicrobial agents	9 (7.8%)
Five antimicrobial agents	3 (2.6%)
Six antimicrobial agents	3 (2.6%)
Seven antimicrobial agents	2 (1.7%)

Table 5: List of Antimicrobial agents prescribed to the study population

Antimicrobial Agents	No. of Patients (%)
Cefuroxime	7 (6.1)
Ceftriaxone	7 (6.1)
Piperacillin/Tazobactam	3 (2.6)
Amoxicillin	2 (1.7)
Clindamycin	2 (1.7)
Azithromycin + Oseltamivir + Cefuroxime + Ceftriaxone	1 (0.9)
Azithromycin + Oseltamivir + Piperacillin / Tazobactam	4 (3.5)
Azithromycin + Cefuroxime + Piperacillin / Tazobactam	2 (1.7)
Clindamycin + Piperacillin / Tazobactam	5 (4.3)
Ceftriaxone + Metronidazole	2 (1.7)
Azithromycin + Oseltamivir + Piperacillin / Tazobactam + Levofloxacin + Amoxicillin / Clavulanic acid	1 (0.9)
Clindamycin + Amoxicillin / Clavulanic acid	1 (0.9)
Oseltamivir + Piperacillin / Tazobactam	2 (1.7)
Cefixime	1 (0.9)
Ceftriaxone+ Clindamycin+ Cefoperazone / Sulbactam	1 (0.9)

Isoniazid+ Rifampin+ Ethambutol+ Pyrazinamide	1 (0.9)
Azithromycin+ Ceftriaxone+ Metronidazole+ Isoniazid+ Rifampin+ Ethambutol+ Pyrazinamide	1 (0.9)
Metronidazole + Piperacillin / Tazobactam	1 (0.9)
Cefoperazone / Sulbactam	10 (8.7)
Ceftriaxone+ Doxycycline	3 (2.6)
Azithromycin+ Doxycycline+ Oseltamivir+ Piperacillin / Tazobactam	1 (0.9)
Cefepime	1 (0.9)
Doxycycline	1 (0.9)
Azithromycin+ Ceftriaxone+ Piperacillin / Tazobactam	1 (0.9)
Ceftriaxone+ Imipenem/ Cilastatin+ Piperacillin / Tazobactam	1 (0.9)
Clindamycin+ Doxycycline+ Meropenem/Sulbactam+ Piperacillin/ Tazobactam+ Teicoplanin+ Vancomycin	1 (0.9)
Azithromycin+ Ceftriaxone+ Oseltamivir+ Cefazolin+ Linezolid+ Doxycycline+ Vancomycin	1 (0.9)
Azithromycin+ Ceftriaxone	6 (5.2)
Azithromycin+ Doxycycline+ Piperacillin / Tazobactam	1 (0.9)
Azithromycin+ Ceftriaxone+ Oseltamivir	6 (5.2)
Cefoperazone/ Sulbactam+ Meropenem/ Sulbactam	1 (0.9)
Ceftriaxone+ Levofloxacin+ Oseltamivir	1 (0.9)
Clindamycin+ Meropenem / Sulbactam	1 (0.9)
Azithromycin+ Ceftriaxone+ Oseltamivir+ Piperacillin / Tazobactam	1 (0.9)
Azithromycin+ Amoxicillin/ Clavulanic acid+ Piperacillin/ Tazobactam+ Meropenem/ Sulbactam	1 (0.9)
Azithromycin+ Oseltamivir+ Meropenem/ Sulbactam+ Piperacillin/ Tazobactam	1 (0.9)
Azithromycin+ Cefuroxime+ Oseltamivir+ Piperacillin/ Tazobactam	1 (0.9)
Amoxicillin/ Clavulanic Acid+ Ciprofloxacin	1 (0.9)
Amoxicillin/ Clavulanic acid+ Clindamycin+ Ciprofloxacin+ Metronidazole+ Piperacillin/Tazobactam+ Tinidazole	1 (0.9)
Ceftriaxone+ Clindamycin	1 (0.9)
Clindamycin+ Fluconazole+ Linezolid+ Meropenem/Sulbactam+ Oseltamivir	1 (0.9)
Azithromycin+ Piperacillin / Tazobactam	3 (2.6)
Azithromycin + Cefuroxime	1 (0.9)
Ceftriaxone+ Meropenem / Sulbactam	1 (0.9)
Ceftriaxone+ Cefoperazone / Sulbactam	2 (1.7)

Azithromycin+ Amoxicillin/ Clavulanic acid+ Levofloxacin	1 (0.9)
Clindamycin+ Linezolid+ Piperacillin/ Tazobactam	1 (0.9)
Amikacin+ Ceftriaxone+ Piperacillin / Tazobactam	1 (0.9)
Imipenem/ Cilastatin+ Linezolid+ Minocycline+ Oseltamivir+ Piperacillin/ Tazobactam+ Sulfamethoxazole/ Trimethoprim	1 (0.9)
Azithromycin+ Ceftriaxone+ Meropenem/ Sulbactam	1 (0.9)
Cefoperazone/ Sulbactam+ Teicoplanin+ Vancomycin	1 (0.9)
Azithromycin+ Linezolid+ Piperacillin / Tazobactam	1 (0.9)
Sulfamethoxazole/ Trimethoprim	1 (0.9)
Azithromycin+ Ceftriaxone+ Itraconazole+ Linezolid+ Piperacillin/ Tazobactam	1 (0.9)
Azithromycin+ Meropenem/ Sulbactam+ Piperacillin/ Tazobactam	1 (0.9)
Meropenem/ Sulbactam	2 (1.7)
Cefoperazone/ Tazobactam	1 (0.9)
Ceftriaxone+ Ceftazidime	1 (0.9)
Doxycycline+ Meropenem+ Teicoplanin+ Piperacillin/ Tazobactam	1 (0.9)
Cefoperazone/ Sulbactam+ Metronidazole	1 (0.9)
Cefoperazone/Sulbactam+ Clindamycin	1 (0.9)
Cefazolin	1 (0.9)
Ceftriaxone+ Sulfamethoxazole+ Trimethoprim	1 (0.9)
Azithromycin+ Ceftriaxone+ Piperacillin/ Tazobactam+ Meropenem/ Sulbactam	1 (0.9)

4.6 Antimicrobials with Potential to Develop Adverse Mental Health in Geriatrics

Total 178 antimicrobial agents with potential to develop adverse mental health were prescribed in 89 geriatric patients. This comprises 21 antimicrobial drugs from various classes of antimicrobial agents.

Majority of the patients were prescribed with Piperacillin/ Tazobactam (40; 22.5%) and Azithromycin (40; 22.5%), followed by Oseltamivir (22;12.4 %) and other antimicrobials [Table 6].

Table 6: Antimicrobial Prescription with Potential to Develop Adverse Mental Health in Geriatrics

Sl. No.	Antimicrobial agents	No. of Antimicrobial Agents
1.	Amoxicillin/ Clavulanic acid	08 (4.5 %)
2.	Piperacillin/ Tazobactam	40 (22.5 %)
3.	Doxycycline	09 (5.1 %)
4.	Minocycline	01 (0.6 %)
5.	Cefazolin	02 (1.1 %)
6.	Cefepime	01 (0.6 %)
7.	Ceftazidime	01 (0.6 %)
8.	Cefuroxime	12 (6.7 %)
9.	Ciprofloxacin	02 (1.1 %)
10.	Levofloxacin	03 (1.7 %)
11.	Azithromycin	40 (22.5 %)
12.	Sulfamethoxazole/Trimethoprim	03 (1.7 %)
13.	Imipenem/ Cilastatin	02 (1.1 %)
14.	Meropenem/ Sulbactam	13 (7.3 %)
15.	Linezolid	06 (3.4 %)
16.	Metronidazole	06 (3.4 %)
17.	Isoniazid	02 (1.1 %)
18.	Rifampin	02 (1.1 %)
19.	Ethambutol	02 (1.1 %)
20.	Fluconazole	01 (0.6 %)
21.	Oseltamivir	22 (12.4 %)

4.7 Combination of Antimicrobials with Potential to Cause Adverse Mental Health in Geriatrics

Out of 115 geriatric patients, 89 (77.4%) patients received antimicrobial agents with potential to cause adverse mental health while 26 (22.6%) patients did not receive such drugs.

The geriatric patients were prescribed these antimicrobial agents as monotherapy 43 (37.4%) or in combination. [Table 7].

Table 7: Combination of Antimicrobials with Potential to Cause Adverse Mental Health in Geriatrics

No. of drugs in combination of Antimicrobials	No. of Patients (%)
No antimicrobial agent	26 (22.6%)
Single Antimicrobial agent	43 (37.4%)
Two Antimicrobial agents	18 (15.7%)
Three Antimicrobial agents	18 (15.7%)
Four Antimicrobial agents	06 (5.2%)
Five Antimicrobial agents	03 (2.6%)
Six Antimicrobial agents	01 (0.9%)

4.8 Prevalence of Adverse Mental Health in Geriatrics

Out of 115 geriatric patients, 10 (8.7%) patients developed adverse mental health after taking the prescribed antimicrobial agents, while 105 (91.3%) patients did not develop ADR [Figure 3].

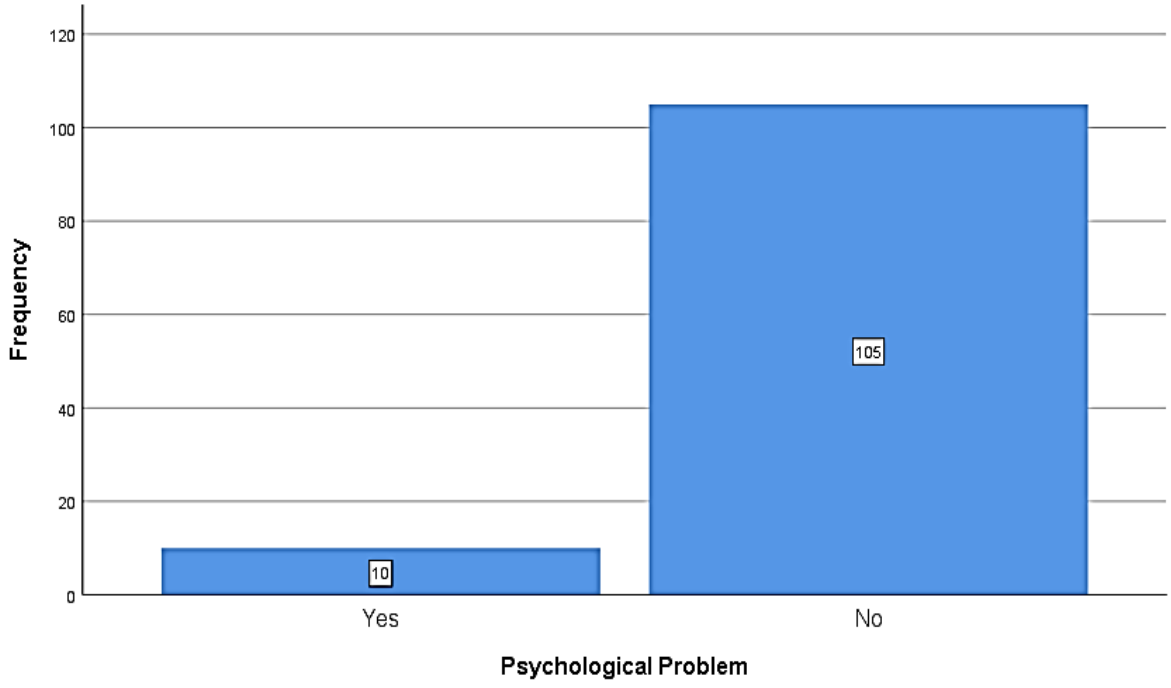

Figure 3: Prevalence of Adverse Mental Health in Geriatrics

4.9 Antimicrobial Prescriptions with potential to cause adverse mental health in geriatrics

Out of total 115 patients, 89 (77.4%) geriatric patients received antimicrobial agents which have the potential to develop adverse mental health [Table 8].

Table 8: Number of Antimicrobial Prescriptions with Potential to Cause Adverse Mental Health in Geriatrics

Antimicrobial prescriptions with potential to cause adverse mental health in geriatrics	No. of Patients
Yes	26 (22.6%)
No	89 (77.4%)

4.10 Antimicrobial Prescriptions with Adverse Mental Health in Geriatrics

Out of 89 geriatric patients who received antimicrobial agents which have potential to cause adverse mental health issues, 10 (11.24%) patients developed the ADRs [Figure 4].

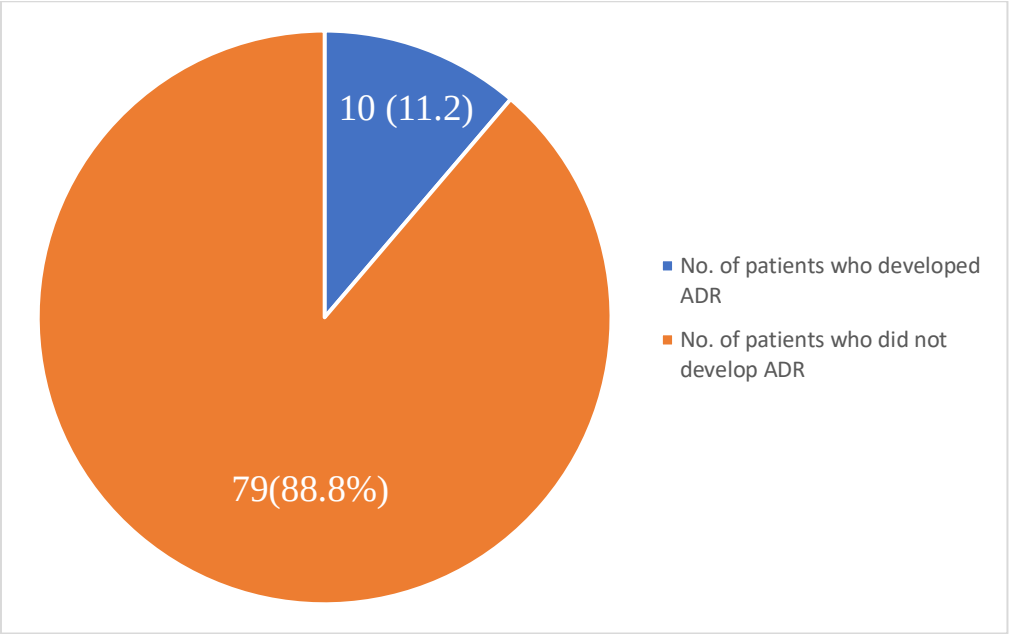

Figure 4: Geriatric Patients with Adverse Mental Health After Antimicrobial Use

4.11 Antimicrobial Agents and the Developed Adverse Mental Health in Geriatrics

Six antimicrobial agents caused the adverse mental health in 10 (11.24%) geriatrics patients among 89 patients who received antimicrobial agents with potential to cause adverse mental health effects.

Out of these 10 patients, 8 patients developed adverse mental health due to single drug, while, 2 patients developed with two and three adverse effects respectively, due to combination of antimicrobial agents [Table 9].

Table 9: Antimicrobial Agents and the Developed Adverse Mental Health in Geriatrics

Antimicrobial agents	Adverse Mental Health	No. of Patients
Azithromycin	Insomnia	2 (2%)
Azithromycin	Agitation	1 (1%)
Metronidazole	Insomnia	2 (2%)
Piperacillin/ Tazobactam	Insomnia	1 (1%)
Piperacillin/ Tazobactam	Delirium	1 (1%)
Oseltamivir	Anxiety	3 (3%)
Oseltamivir	Nightmares	1 (4%)
Doxycycline	Insomnia	1 (1%)
Meropenem/ Sulbactam	Seizures	1 (1%)

4.12 Antipsychotic Drugs Prescribed for Adverse Mental Health

Out of 89 geriatric patients, 10 (11.24%) patients developed adverse mental health. Of these, 4 patients received antipsychotic drugs for treatment of adverse mental health related to antimicrobial agents [Table 10].

Table 10: Antipsychotic Drugs Prescribed for Adverse Mental Health

Adverse Mental Health	Antipsychotic drug
Insomnia	Alprazolam, Zolpidem
Delirium	Quetiapine
Seizures	Lorazepam

4.13 Average Number of Antimicrobial Agents per Prescriptions

In our geriatric patients, average number of antimicrobials per prescription is 2.3.

4.14 Average Number of Antimicrobial Agents per Prescriptions with Potential to Cause Adverse Mental health

In our geriatric patients, average number of antimicrobials per prescription, which has the potential to cause mental health adverse effect is 1.5.

4.15 Risk estimation for development of the Adverse Mental Health with Gender

In our study, 10 patients developed ADR, out of which 8 (12.5%) were females and 2 (3.9%) were male.

Table 11: Association between Gender and Adverse Mental Health

Gender	ADR	No ADR	Total	Risk estimation
Female	8 (12.5%)	56 (87.5%)	64 (100%)	**OR: 3.5 95%CI:0.71-17.27**
Male	2 (3.9 %)	49 (96.1%)	51 (100%)	
Total	10 (8.7%)	105 (91.3%)	115 (100%)	

Female geriatric patients have 3.5 times higher risk for developing the adverse mental health problems compared to male patients after the antimicrobial use (OR: 3.5; 95%CI:0.06-1.41) [Table 11]

4.16 Risk estimation for development of the Adverse Mental Health with Renal Dysfunction

Table 12: Association between Renal Dysfunction and Adverse Mental Health

Renal dysfunction	ADR	No ADR	Total	Risk estimation
Yes	1 (6.7 %)	14 (93.3 %)	15 (100%)	**OR: 0.28 95%CI:0.08-6.15**
No	9 (9.0 %)	91 (91.0 %)	100 (100%)	
Total	10 (8.7%)	105 (91.3%)	115 (100%)	

The risk for development of adverse mental health problems in patients with renal dysfunction are 28% times less likely than the patients with normal renal function (OR: 0.28; 95%CI:0.08-6.15) [Table 12]. This may be because number of patients with renal dysfunction in our study population is very small.

DISCUSSION

5. DISCUSSION

A cross-sectional study was conducted in Kasturba Hospital, Manipal to evaluate antimicrobial agents with potential to develop adverse mental health in geriatrics. This study comprised of 115 geriatric patients (age 65 years and above) prescribed with antimicrobial agents. Informed consent was obtained from the patients or legally authorized representatives (unresponsive patients). The data was collected from the medical records and the direct patients interview form all the Medicine units of the hospital. In our knowledge, not much studies are performed on mental health, especially on the drug-induced adverse mental health in Indian population.

In our study, the age of the patients was 65 years and above, as it involved only geriatric patients. The mean age of our study population was found to be 71.90 ± 6.186 years. According to a randomized controlled trial (RCT) by Avni et al [(8)], no RCT reported exclusion based on an upper age limit in geriatric trials. Mattappalil et al [(4)] have suggested that the risk of developing neurotoxicity symptoms was more in elderly patients due to various age-related changes.

This study included total of 115 patients, out which 51 (44.3%) were male and 64 (55.7%) were female. The number of female patients is higher than male as female wards were visited more than the male wards for data collection. The mean duration of hospitalization for this study was found to be 11.82 ± 6.96 days. There was no significant relation found between increased duration of hospitalization and occurrence of adverse drug reactions (ADRs). Also, alcoholism and smoking had no significant effect on occurrence of ADRs. The mean number of co-morbidities found in our study population was 1.74 ± 1.33.

Respiratory tract infections such as pneumonia (25; 21.73%) and LRTI (21; 18.26%) were most common conditions for prescription of antimicrobial agents. The second most common condition was UTI (11;9.56%) and urosepsis (9; 7.82%), followed by suspected infections (13; 11.3%) and other conditions (36; 31.3%). Apisarnthanarak A, et al. [(9)] also reported almost similar finding where RTI were the most common conditions leading to antibiotic prescription. The second most common condition was UTI followed by gastrointestinal tract infections, fever and suspected tract infections and others.

The average number of antibiotics per prescription is an important index of the scope for review and educational intervention in prescribing habits. In this study, the average number of antibiotics per prescription was found to be 2.3. Based on result of prescription analysis, most

of the patients received monotherapy (39;33.9%), followed by 2 antimicrobial agents (34; 29.6%), 3 antimicrobial agents (25;21.7%) and more than 3 antimicrobial agents (7; 14.7 %). Similar result was reported by Bist et al. [(10)], where monotherapy (60%), 2 drugs (27%), 3 drugs (11.06%), 4 drugs (1.40%) received by study participants.

The indications for antimicrobial use was divided into two empiric and definitive. Prescriptions were considered empiric if: (a) it was mentioned in medical record as empiric treatment, (b) an infectious disease was diagnosed, (c) clinical signs and symptoms of infection such as fever were present on the day of starting antimicrobial therapy. Prescriptions were considered as definitive if: (a) it was mentioned in medical record, (b) antimicrobial agents were initiated after culture test. In our study, out of total 115 geriatric patients, 45 (39.1%) patients received empirical antimicrobial agents while, 70 (60.9%) received definitive treatment of antimicrobial agents based on their diagnosis. Apisarnthanarak et al. [(9)] analysed the impact on five reasons for inappropriateness of prescribing antibiotics. These include inappropriate surgical prophylaxis, use of antibiotic without any evidence of infection, redundant spectrum, bacterial resistance and narrow spectrum was available. Warstler et al [(3)] observed that the antimicrobial induced adverse mental health is supported by limited number of case reports and case series. Data from large, randomized-controlled studies are lacking.

A checklist of antimicrobial agents which have potential to develop adverse mental health issues in geriatrics was prepared [Table 1]. Out of total 115 patients in our study, 89 (77.4%) geriatric patients received antimicrobial agents which have the potential to develop adverse mental health. Of these 89 patients, 10 (11.24%) patients developed adverse mental health effects. On an average, 1.5 antimicrobial agent with potential to cause ADR was prescribed per prescription. Majorly prescribed antimicrobials with potential to cause adverse mental health in the study population were Piperacillin/ Tazobactam (40; 22.5 %) among the beta-lactam class, Azithromycin (40; 22.5 %) among the macrolide class, Oseltamivir (22; 12.4 %) among the antiviral class, Meropenem/Sulbactam(13; 7.3%) among the carbapenem class and Cefuroxime (12; 6.7%) among the cephalosporin class.

Total 178 antimicrobial agents with potential to develop adverse mental health were prescribed in 115 geriatric patients. These included 21 drugs from different class of antimicrobial agents. In the beta-lactam class, Amoxicillin/ Clavulanic acid 08 (4.5%) and Piperacillin/ Tazobactam 40 (22.5%) were present. Mattappalil et al reported that although beta-lactams are considered as safe for administration on geriatrics, but the neurotoxicity with Penicillin/ Tazobactam is

more prevalent in geriatrics as per a review article [4]. According to a systematic review by Sutter et al [11], Piperacillin/ Tazobactam has been reported to cause seizures in patients with renal insufficiency. Among the tetracycline class of antimicrobials were Doxycycline (9; 5.1%) and Minocycline (1; 0.6%). According to a case report by Atigari et al [12], two of three patients committed suicide while on Doxycycline treatment. While Shamout et al [13] presents a case of a female diagnosed with perioral dermatitis treated with Minocycline developed severe depersonalization symptoms within 1 week after initiation of the drug.

Among the cephalosporin class of antimicrobials there were four drugs namely, Cefazolin (02; 1.1%), Cefuroxime (12; 6.7%), Ceftazidime (1; 0.6%) and Cefepime (1; 0.6%). Grill et al [14] reported neurotoxicity with first-generation (e.g. cefazolin), second generation (e.g. cefuroxime), third generation (e.g. ceftazidime) and fourth generation (e.g. cefepime) cephalosporins. These adverse effects range from encephalopathy to non-convulsive status epilepticus. A systematic review by Payne et al [15] revealed 135 patients who received cefepime exhibited altered mental status with declined consciousness (47%), myoclonus (42%), and confusion (42%). Another systematic review by Sutter et al [11] found cephalosporins have been reported to cause seizures in patients with renal insufficiency.

Ciprofloxacin (2;1.1%) and Levofloxacin (3; 1.7%) were among the fluoroquinolones. Sellick et al [16] suggested that delirium or psychosis occurred in 3.6% (n=23) of the study population due to Ciprofloxacin. Tome et al [17] found out of 111 ADRs, common were mania (38 cases), insomnia (10 cases), acute psychosis (8 cases), delirium (8 cases), seizures (23 cases) and confusion (9 cases) due to Ciprofloxacin, while, Levofloxacin caused delirium (8 cases).

Azithromycin (40; 22.5%) was one of the majorly prescribed antimicrobial agents among the macrolide class. Cone et al [18] reported two geriatric patients (aged 78 years and 88 years) have developed delirium within 72 hours after initiating Azithromycin therapy. The symptoms lasted 48 to 72 hours after discontinuing the drug. Sulfonamides class Sulfamethoxazole-Trimethoprim 03 (1.7%) was one of the potent antimicrobial agents prescribed to these patients. Gregor et al [19] reported that a 74-year-old woman developed visual hallucinations and delusions over a six-day period after oral administration of the drug for UTI. After 60 hours of discontinuation of drug, her mental functioning returned to normal. Another case report by Stuhec [20] found that an 86-year-old woman developed hallucinations when treated with sulfamethoxazole-trimethoprim for UTI.

Among the carbapenem class, two drugs were prescribed namely, Imipenem-Cilastatin (2; 1.1%) and Meropenem/Sulbactam (13; 7.3%). A systematic review by Sutter et al [11] reported Imipenem found to be more seizure-inducing than meropenem. Linezolid (6; 3.4%) belongs to Oxazolidinone class of antimicrobial agents. Mattappalil et al [4] found incidence of neurotoxicity with linezolid is low (0.36%), whereas, encephalopathy and delirium incidence are high.

Other antibiotics such as Metronidazole (6 ;3.4%), Isoniazid (2; 1.1%), Rifampin (2; 1.1%), and Ethambutol (2; 1.1%) were also prescribed. Papathanasiou et al [21] published a case report with a 62-year-old male who developed reversible encephalopathy due to Metronidazole, while Kim et al [22] published a case of 71-year-old Asian man developed encephalopathy post metronidazole therapy for infectious colitis. A review article by Zareifopoulos [23] suggested that though many cases of Isoniazid-induced mania or toxic psychosis have been reported but it is not likely to be mediated by specific action of the drug in the CNS. Denholm et al [24] reported that 9 patients developed cognitive impairment, 1 patient reported of sleep disturbance, while 1 patient reported to have developed psychosis, paranoia and hallucination after a month of initiating the Isoniazid therapy. A review article by Zareifopoulos et al [25] suggested that incidents of Rifampin-induced neurotoxicity are reported but are rare. Incidents of ethambutol induced psychosis and mania are also reported.

Among the antifungal class of antimicrobial agents, only Fluconazole (1; 0.6%) was prescribed in the study population. Matsumoto, et al [25] published two case reports of Fluconazole induced seizures in a 66-year-old woman and 62-year-old man, respectively. Besides, Govindarajan et al [26] reported Fluconazole- induced seizures, insomnia, and somnolence.

Among the antiviral class of drug, only Oseltamivir (22;12.4%) was prescribed in the study population. Chen R, et al [27] published a case report with 57-year-old female suffered from hallucinations, delirium and unusual behaviour following Oseltamivir therapy, but recovered completely after cessation of the therapy.

The antimicrobial agents with potential to develop adverse mental health in geriatrics were prescribed as monotherapy (43; 37.4%) or in combinations like 2 drugs (18 ;15.7%), 3 drugs (18;15.7%), more than 3 drugs (10;8.7%). On an average, 1.5 antimicrobial agent with potential to cause adverse mental health was prescribed per prescription.

The 10 patients who developed the adverse effects were prescribed with Azithromycin (insomnia= 2, agitation = 1), Metronidazole (insomnia = 2), Piperacillin-Tazobactam

(insomnia = 1, delirium =1), Oseltamivir (anxiety = 3, nightmare = 1), Doxycycline (insomnia =1), Meropenem-Sulbactam (seizures = 1). Out of these 10 patients who developed adverse mental health, 3 patients received anti-psychotic drugs such as Alprazolam and Zolpidem for insomnia, Quetiapine for delirium and Lorazepam for seizures.

Risk estimation shows that female geriatric patients have 3.5 times higher risk for developing the adverse mental health problems compared to male patients after the antimicrobial use. Rademaker, (2001) reported that female has 1.5 to 1.7 times higher of developing an ADR than male [(28)]. This may be due to gender differences in hormonal as well as immunological physiology that modulate PK/PD response [(29)]. Unlike other studies the risk for development of adverse mental health problems in patients with renal dysfunction are 2.8 times less likely than the patients with normal renal function.

CONCLUSION

6. CONCLUSION

The study concludes that majority of geriatric patients were prescribed antimicrobial agents that have potential to develop adverse mental health issues. The geriatric population is already at a greater risk of developing drug induced neuropsychiatric adverse effects due to various age-related factors. It is also important to note that majority of antimicrobial agents induced neuropsychiatric or adverse mental health problems are supported by case reports or case series only. Data from large, randomized-controlled studies are lacking. Not many studies have been performed on the drug-induced mental health in Indian population. However, various antimicrobial classes are involved in adverse mental health issues in geriatrics such as beta-lactams, tetracyclines, cephalosporins, fluoroquinolones, macrolides, sulfonamides, aminoglycosides, carbapenems, oxazolidines, other antibiotics, antifungals, antimalarial and antivirals. Risk estimation shows that women geriatric patients have higher risk for developing the adverse mental health problems compared to men after the antimicrobial use. However, unlike other studies renal dysfunction was not found to be a risk factor for developing the adverse mental health. Potential mechanism of toxicity differs among the agents and the etiology also remains unidentified in some cases. Incidence of adverse mental health is increased due to presence of co-morbidities or drug interaction. Therefore, prior to prescribing these antimicrobial agents, certain aspects should be taken into consideration such as drug dosing, co-morbidities, concurrent medication use and baseline clinical characteristics. Use of antimicrobial agents without concern for age-related alterations potentiates the risk of adverse mental health in geriatric patients. Awareness of antimicrobials contributing to neuropsychiatric events may enhance clinical decisions in diagnosis and management when such incidents occur.

LIMITATIONS

7. LIMITATIONS

a) We have included cases from only medicine units of Kasturba Medical College Hospital since the infectious disease cases are admitted mainly in medicine units.
b) Not all the drugs included in the checklist were observed due to decreased prescribing of those drugs in our hospital.
c) The ADRs are not reported in the medical records for most of the patients and the patients are also not aware about the unusual symptoms or do not share the same with physicians due to social stigma.

BIBLIOGRAPHY

8. REFERENCES

1. Mody L. Approach to infection in older adult. UpToDate: 1-17. Available from: https://www.uptodate.com/contents/approach-to-infection-in-the-older-adult#H340135614
2. Giarratano A, Green SE, Nicolau DP. Review of antimicrobial use and considerations in the elderly population. Clin Interv Aging. 2018; 13:657-667.
3. Warstler A, Bean J. Antimicrobial-induced cognitive side effects. Ment Health Clin. 2016;6(4):207-214.
4. Mattappalil A, Mergenhagen KA. Neurotoxicity with antimicrobials in the elderly: a review. Clin Ther. 2014;36(11):1489-1511.e4.
5. Charach G, Argov O, Nochomovich H, Geiger K, Charach L, et al. Cephalosporin-induced Neurological Toxicity in Elderly Patients with Preserved Renal Function. Arch Med. 2016, 8:6.
6. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects;1-3. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics.
7. Highlights of prescribing information to use meropenem for injection USP and sodium chloride injection USP safely and effectively. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205883Orig1s000lbl.pdf.
8. Avni T, Shiver-Ofer S, Leibovici L, et al. Participation of elderly adults in randomized controlled trials addressing antibiotic treatment of pneumonia. J Am Geriatr Soc. 2015;63(2):233-243.
9. Apisarnthanarak A, Danchaivijitr S, Khawcharoenporn T, et al. Effectiveness of education and an antibiotic-control program in a tertiary care hospital in Thailand. Clin Infect Dis. 2006;42(6):768-775.
10. Bist A, Kulkarni GP, Gumma KM. Study of patterns of prescribing antibiotics in geriatric patients admitted to the medical wards in a tertiary care hospital. International Journal of Basic & Clinical Pharmacology 2016;5(1): 155-158.

11. Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs: A systematic review. Neurology. 2015;85(15):1332-1341.
12. Atigari OV, Hogan C, Healy D. Doxycycline and suicidality. BMJ Case Rep. 2013;2013: bcr2013200723.
13. Shamout Y, Sigal A, Litvinov IV. Minocycline-induced transient depersonalization: A case report. SAGE Open Med Case Rep. 2019; 7:2050313X18823827.
14. Grill MF, Maganti R; Cephalosporin-induced Neurotoxicity: Clinical Manifestations, Potential Pathogenic Mechanisms, and the Role of Electroencephalographic Monitoring; Infectious Diseases, The Annals of Pharmacotherapy, 2008 December, Vol 42; 1843-1850.
15. Payne LE, Gagnon DJ, Riker RR, et al. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017;21(1):276.
16. Sellick J, Mergenhagen K, Morris L, et al (2017); Fluoroquinolone-Related Neuropsychiatric Events in Hospitalized Veterans; The Academy of Psychosomatic Medicine; 1-8.
17. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf. 2011;34(6):465-488.
18. Cone LA, Padilla L, Potts BE. Delirium in the elderly resulting from azithromycin therapy. Surg Neurol. 2003;59(6):509-511.
19. Gregor JC, Zilli CA, Gotlib IH. Acute psychosis associated with oral trimethoprim-sulfamethoxazole therapy. Can J Psychiatry. 1993;38(1):56-58..
20. Stuhec M. Trimethoprim-sulfamethoxazole-related hallucinations. Gen Hosp Psychiatry. 2014;36(2).
21. Papathanasiou A, Zouvelou V, Kyriazi S, Rentzos M, Evdokimidis I. Metronidazole-induced reversible encephalopathy in a patient with facioscapulohumeral muscular dystrophy. Clin Neuroradiol. 2013;23(3):217-219.
22. Kim H, Kim YW, Kim SR, Park IS, Jo KW. Metronidazole-induced encephalopathy in a patient with infectious colitis: a case report. J Med Case Rep. 2011; 5:63.
23. Zareifopoulos N, Panayiotakopoulos G. Neuropsychiatric Effects of Antimicrobial Agents. Clin Drug Investig. 2017;37(5):423-437.

24. Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C, Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. *Drug Healthc Patient Saf*. 2014; 6:145-149.
25. Matsumoto K, Ueno K, Yoshimura H, et al. Fluconazole-induced convulsions at serum trough concentrations of approximately 80 microg/mL. Ther Drug Monit. 2000;22(5):635-636.
26. Govindarajan A, Bistas KG, Aboeed A. Fluconazole. StatPearls. NCBI Bookshelf. 2020 April 3. StatPearls Publishing.
27. Chen R, Fang Z, Huang Y. Neuropsychiatric events in an adult patient with influenza a (H3N2) treated with oseltamivir (Tamiflu): a case report. BMC Infect Dis. 2019; 19: 224.
28. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol. 2001. 2: 349-351.
29. Soldin O, Chung S, Mattison D. Sex differences in drug disposition. J Biomed Biotechnol. 2011: 187103.

APPENDICES

Appendix I: Institutional Ethics Clearance Certificate

KASTURBA HOSPITAL
MANIPAL
(An associate Hospital of MAHE, Manipal)

Kasturba Medical College and Kasturba Hospital
Institutional Ethics Committee
(Registration No. ECR/146/Inst/KA/2013/RR-16)

Communication of the decision of the Institutional Ethics Committee

Wednesday 14th August 2019 **IEC : 588/2019**

Project title	:	Evaluation of antimicrobial agents with potential to develop adverse mental health in geriatrics.
Principal Investigator	:	Miss. Vaishali V. Shinde
Guide/ Co Guide/ Co Investigators	:	Dr. Sonal Sekhar, Levine M Wilson, Dr. Kavitha Saravu
Name & Address of Institution	:	Department of Pharmacy Practice, MCOPS, Manipal, Department of Medicine, KMC, Manipal.
Status of review	:	New
Date of review	:	13.08.2019
Decision of the IEC	:	Approved for the study period from 13.08.2019 to 12.08.2020.

- The PI and all members of the project shall ensure compliance to current regulatory provisions (as per Schedule Y of Drugs and Cosmetics Act and ICH-GCP), Ethical Guidelines for Biomedical Research on Human Participants by ICMR, and the SOP of IEC including timely submission of Interim Annual Report and Final Closure Report
- Participant Information Sheet and a copy of signed Informed Consent shall be given to every research participant
- Inform IEC in case of any proposed amendments (change in protocol / procedure, site / Investigator etc)
- Inform IEC immediately in case of any Adverse Events and Serious Adverse Events.
- Members of IEC have the right to monitor any project with prior intimation.
- Ensure registration of this study at Clinical Trials Registry - India (CTRI) before the enrollment of the first participant (The registration number is to be forwarded to the IEC within 7 days of your successful registration).

Dr. Rajeshkrishna Bhandary P
MEMBER SECRETARY - IEC

ETHICS COMMITTEE APPROVED KASTURBA HOSPITAL MANIPAL

IEC Secretariat, Room No. 22, Ground Floor, Faculty Room Complex, Kasturba Medical College Premises,
Kasturba Medical College, Manipal - 576104, Karnataka, India. Phone : +91 - 0820 - 2933522, Fax : +91 - 0820 - 2571927. Email : iec.kmc@manipal.edu

MR-798

(Yoga and Ayurveda services are excluded from the scope of NABH accreditation)

Appendix II a: Participant Information Sheet (English)

PARTICIPANT INFORMATION SHEET

Project title: Evaluation of antimicrobial agents with potential to develop adverse mental health in geriatrics
IEC No.: 588/2019
Sponsor Name:
Language: English

Principal Investigator: Vaishali V. Shinde
Designation: 2nd year Pharm-D (PB)
Hospital: Kasturba Medical College Hospital, Manipal
Mobile number: 8108134431

Please read this form carefully. If you don't understand the language or any information in this document, please discuss with study doctor. Your participation in this study is voluntary, and you can enquire about all details before giving your written consent to participate in this study.

1. **Introduction to the research study:**

You are invited to participate in this study because you belong to geriatric age group who have been prescribed antimicrobials.

2. **Purpose of the study:**

The purpose of this study is to:

(a) To prepare a checklist of drugs as per the hospital formulary, which have the potential to cause adverse mental health.

(b) Evaluate the geriatric antimicrobial prescription to determine its potential to cause mental health issue.

(c) To identify antimicrobial related mental health problems in geriatric patients.

3. **Who can take part:**

Inclusion criteria:

- Geriatric patients
- Patients of both gender
- Patients receiving antimicrobial drugs

Exclusion criteria:

- Geriatric patients who have not been prescribed antimicrobial drugs
- Other than geriatric population
- Patients who have psychiatric disorder or on anti-psychotic drugs

4. **Information about the study (as a whole):**

300 geriatric patients admitted in the medicine units of KMC hospital, who have been prescribed antimicrobial drugs will be included in the study. The prescriptions will be evaluated by the investigator and checked for antimicrobial drugs that have potential to cause adverse mental health. The study period is of one year.

5. **What will happen to you (the individual participant) during the study:**

Since it is an observational study, the prescriptions will be evaluated from your patient medical file. Also, please provide information as enquired by the investigator or physician. Your identity will remain confidential. The approximate time taken for the data collection would be 30 minutes. The prescriptions will be evaluated as per geriatric guidelines and checked for antimicrobials which have potential to cause adverse mental health.

6. **Your (the individual participant) role/responsibility in the study:**

- Provide accurate information whenever asked.
- Inform the study doctor about any problem/side effects experienced during the study.
- If you want to discontinue from the study, study doctor to be informed.

7. **What are the risks?**

Since this is an observational study, only a minimal risk is involved.

8. **What are the potential benefits of participating in the study:**

You may or may not get benefit from participating in this study. It is possible that you may get better, stay the same, or get worse. If you take part in this study you may help other patients by helping to collect evidence of drugs that can cause potential adverse mental health issues in geriatric population, thereby, by contributing to the knowledge on the drugs prescribed for geriatric patients.

9. **What are the alternative treatments available?**

Since the study is observational in nature, study does not influence any treatment.

10. **Cost of participating in the study:**

No additional costs for being a part of the study.

11. **Compensation for injury:**

Since this is an observational study, no medical problem will arise due to this study.

12. **Confidentiality of information:**

Information from the study records including your name, address, medical records, results of tests, study results will be kept confidential and will be reviewed only by authorized personnel from the sponsor or their representative, Ethics Committee or regulatory bodies. The data will not be made available to another individual unless you specifically give permission in writing. Information and results from this study may be presented at meetings or published in journals without including your name and personal identifications. No reference will be made in oral or written reports which could link you to the study.

13. **New information about the study:**

Any new information available during the course of the study will be informed to you if it has relevance to your decision regarding continuing in the study. Results of your participation will be disclosed to you if you indicate your desire for it.

14. **Voluntary participation:**

Your participation in this study is voluntary; you may decline to participate at any time and you need not give any reason for the same, and such withdrawal shall be without penalty and without loss of benefits to which you are otherwise entitled. If you withdraw from the study prior to its completion, you will receive the usual standard of care for your disease, and your non-participation will not have any adverse effects on your subsequent medical treatment or relationship with the treating physician.

If you withdraw from the study before data collection is completed, your data collected until you indicated withdrawal will be used in the study report. Sponsor or the investigator may stop the research or your participation in it at any time for some or other reason without your permission.

15. **Whom to contact in case of any questions:**

If you experience adverse effects as a result of participating in this study, you may contact the Principal Investigator (Vaishali V. Shinde) as detailed above.

If you have any questions about the informed consent process or your rights as a participant, you may contact the Member Secretary of the Kasturba Medical College and Kasturba Hospital - Institutional Ethics Committee at Room 22, Ground floor, KMC Faculty Rooms, adjacent to KMC Administrative Block, Kasturba Medical College, Manipal - 576104. Phone: 0820 29 33522. Timings: 9:00 AM to 5:00 PM.

If you have any questions about this form or any study related issue, you may also contact the following person.

Name**:** Dr. Rajesh V.
Address**:** Department of Pharmacy Practice, MCOPS, Manipal
Telephone No.**:** +919538417313

Appendix II b: Participant Information Sheet (Kannada)

ಭಾಗೀದಾರರ ಮಾಹಿತಿ ಪತ್ರ

ಅಧ್ಯಯನದ ಹೆಸರು: ವಯೋವೃದ್ಧರಲ್ಲಿ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯಿಂದ ಸಂಭಾವ್ಯ ಪ್ರತಿಕೂಲ ಮಾನಸಿಕ ಆರೋಗ್ಯದ ಬೆಳವಣಿಗೆಯ ಮೌಲ್ಯಮಾಪನ.

ಅಧ್ಯಯನದ ಸಂಖ್ಯೆ:

ಪ್ರಾಯೋಜಕರು:

ಭಾಷೆ: ಕನ್ನಡ

ಮುಖ್ಯ ಸಂಶೋಧಕರು: ವೈಶಾಲಿ ವಿ. ಶಿಂಧೆ.

ಹುದ್ದೆ: 2ನೇ ವರ್ಷದ ಬಿ.ಫಾರ್ಮಾ(ಪಿಬಿ)

ಆಸ್ಪತ್ರೆ: ಕಸ್ತೂರ್ಬಾ ವೈದ್ಯಕೀಯ ಕಾಲೇಜು ಆಸ್ಪತ್ರೆ, ಮಣಿಪಾಲ.

ದೂರವಾಣಿ ಸಂಖ್ಯೆ: 8108134431

ದಯವಿಟ್ಟು ಈ ಮಾಹಿತಿ ಪತ್ರವನ್ನು ಜಾಗರೂಕತೆಯಿಂದ ಓದಿರಿ. ನಿಮಗೆ ಇದರಲ್ಲಿನ ಭಾಷೆ ಅಥವಾ ಯಾವುದೇ ಮಾಹಿತಿಗಳು ಅರ್ಥವಾಗದೇ ಇದ್ದಲ್ಲಿ, ದಯವಿಟ್ಟು ಅಧ್ಯಯನಕಾರ ವೈದ್ಯರುಗಳ ಜೊತೆಯಲ್ಲಿ ಚರ್ಚಿಸಿರಿ. ಈ ಅಧ್ಯಯನಲ್ಲಿ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯು ಐಚ್ಛಿಕವಾಗಿರುತ್ತದೆ. ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಗೆ ನೀಡುವ ಮೊದಲು ಅಧ್ಯಯನದ ವಿವರಗಳ ಬಗ್ಗೆ ವಿಚಾರಣೆ ಮಾಡಬಹುದು.

1.ಅಧ್ಯಯನದ ಪ್ರಸ್ತಾವನೆ:

ನಿಮ್ಮನ್ನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಆಹ್ವಾಹಿಸುತ್ತಿದ್ದೇವೆ ಏಕೆಂದರೆ, ನೀವು ವಯೋವೃದ್ಧರ ಗುಂಪಿನವರಾಗಿರುವಿರಿ.ನಿಮಗೆ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯನ್ನು ಸೂಚಿಸಲಾಗಿರುತ್ತದೆ.

2. ಅಧ್ಯಯನದ ಉದ್ದೇಶ:

ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶವೇನೆಂದರೆ:

ಎ) ವಯೋವೃದ್ಧರಿಗೆ ಸೂಚಿಸಿರುವ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯಿಂದ ಉಂಟಾಗುವ ಸಂಭಾವ್ಯ ಮಾನಸಿಕ ಸಮಸ್ಯೆಗಳನ್ನು ನಿರ್ಧರಿಸುವುದು ಮತ್ತು ಅದರ ಮೌಲ್ಯಮಾಪನ ಮಾಡುವುದು.

ಬಿ) ವಯೋವೃದ್ಧರಲ್ಲಿನ ಮಾನಸಿಕ ಆರೋಗ್ಯಕ್ಕೆ ಸಂಬಂಧಿಸಿದ ತೊಂದರೆಗಳನ್ನು ಗುರುತಿಸುವುದು.

3. ಅಧ್ಯಯನದಲ್ಲಿ ಯಾರು ಭಾಗವಹಿಸುವರು:

<u>ಒಳಗಿಡುವ ಮಾನದಂಡ:</u>

- ವಯೋವೃದ್ಧ ರೋಗಿಗಳು.
- ಎಲ್ಲಾ ಲಿಂಗದ ರೋಗಿಗಳು.
- ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯನ್ನು ತೆಗೆದುಕೊಳ್ಳುತ್ತಿರುವ ರೋಗಿಗಳು ಪಾಲ್ಗೊಳ್ಳುವರು.

<u>ಹೊರಗಿಡುವ ಮಾನದಂಡ:</u>

- ವಯೋವೃದ್ಧರಾಗಿದ್ದು, ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯನ್ನು ತೆಗೆದುಕೊಳ್ಳದಿರುವ ರೋಗಿಗಳು.
- ವಯೋವೃದ್ಧರಾಗಿರದೇ ಇರುವ ರೋಗಿಗಳು ಭಾಗವಹಿಸುವಂತಿಲ್ಲ.

4.ಅಧ್ಯಯನದ ಬಗ್ಗೆ ಮಾಹಿತಿ (ಸಂಪೂರ್ಣ):

ಕಸ್ತೂರ್ಬಾ ಆಸ್ಪತ್ರೆ ಮಣಿಪಾಲದ ಔಷಧಿ ಘಟಕದಲ್ಲಿ (ಮೆಡಿಸಿನ್ ಯುನಿಟ್)ದಾಖಲಾಗಿರುವ 300 ರೋಗಿಗಳ ಅಧ್ಯಯನ ನಡೆಸಲಾಗುವುದು. ಯಾರಿಗೆ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯನ್ನು ಸೂಚಿಸಲಾಗಿದೆಯೋ ಅಂತಹ ರೋಗಿಗಳನ್ನು ಸೇರ್ಪಡೆ ಮಾಡಿಕೊಳ್ಳಲಾಗುತ್ತದೆ. ನಿಮಗೆ ಸೂಚಿಸಿರುವ ಔಷಧಿಯನ್ನು ಸಂಶೋಧಕರು ಮೌಲ್ಯಮಾಪನ ಮಾಡುತ್ತಾರೆ. ಜಾಗೂ ಸೂಚಿಸಿದ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯ ಪ್ರತಿಕೂಲ ಮಾನಸಿಕ ಆರೋಗ್ಯಕ್ಕೆ ಕಾರಣವನ್ನು ಪರೀಕ್ಷಿಸಲಾಗುವುದು. ಈ ಅಧ್ಯಯನದ ಕಾಲಾವಧಿ ಒಂದು ವರ್ಷ.

5. ಅಧ್ಯಯನದ ಸಂದರ್ಭದಲ್ಲಿ ನಿಮಗೆ ಏನಾಗಬಹುದು:

ಇದುವರೆಗೆ ಇದು ಒಂದು ವೀಕ್ಷಣಾ ಅಧ್ಯಯನವಾಗಿರುತ್ತದೆ. ನಿಮ್ಮ ವೈದ್ಯಕೀಯ ಔಷಧಿಯ ಕಡತದಲ್ಲಿ ರೋಗಿಗೆ ಸೂಚಿಸಿರುವ ಔಷಧಿಯನ್ನು ಮೌಲ್ಯಮಾಪನ ಮಾಡಲಾಗುವುದು. ಅಂತೆಯೇ, ದಯವಿಟ್ಟು ನೀವು ಸಂಶೋಧಕರಿಗೆ ಅಥವಾ ವೈದ್ಯರಿಗೆ ಅವಶ್ಯಕವಾಗಿರುವ ಮಾಹಿತಿಗಳನ್ನು ನೀಡಿರಿ. ನಿಮ್ಮ ವೈಯಕ್ತಿಕ ಗುರುತನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು. ಈ ಎಲ್ಲಾ ಡಾಟಾಗಳನ್ನು ಸಂಗ್ರಹಿಸಲು ಸರಿಸುಮಾರು ೫೦ ನಿಮಿಷಗಳನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು. ವಯೋವೃದ್ಧರ ಚಿಕಿತ್ಸಾ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ಸೂಚಿಸಿರುವ ಔಷಧಿಗಳ ಮೌಲ್ಯಮಾಪನ ಮಾಡಲಾಗುವುದು.ಮತ್ತು ಈ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯಿಂದಾಗುವ ಸಂಭಾವ್ಯ ಪ್ರತಿಕೂಲ ಮಾನಸಿಕ ಆರೋಗ್ಯಕ್ಕೆ ಕಾರಣವನ್ನು ಪರೀಕ್ಷಿಸಲಾಗುವುದು.

6. ನಿಮ್ಮ ಜವಾಬ್ದಾರಿ/ಪಾತ್ರ:

- ಕೇಳಲಾದ ವಿಷಯಕ್ಕೆ ಸರಿಯಾದ ಉತ್ತರವನ್ನು ಕೊಡಬೇಕಾಗುವುದು.
- ನಿಮಗೇನಾದರೂ ತೊಂದರೆ/ವ್ಯತಿರಿಕ್ತ ಪರಿಣಾಮದ ಅನುಭವವಾದಲ್ಲಿ ಅಧ್ಯಯನಕಾರ ವೈದ್ಯರಲ್ಲಿ ತಿಳಿಸಬೇಕಾಗುವುದು.
- ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ನಿಲ್ಲಿಸುವುದಿದ್ದಲ್ಲಿ ಸಂಶೋಧನಾಕಾರರಲ್ಲಿ ತಿಳಿಸಬೇಕಾಗುವುದು.

7. ಅಪಾಯಗಳಾವುವು?.

ಇದುವರೆಗೆ, ಇದು ಒಂದು ವೀಕ್ಷಣಾ ಅಧ್ಯಯನವಾಗಿರುತ್ತದೆ.

8. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವುದರಿಂದ ಆಗಬಹುದಾದ ಸಂಭಾವ್ಯ ಪ್ರಯೋಜನಗಳು:

ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಪ್ರಯೋಜನವನ್ನು ಪಡೆಯಬಹುದು ಅಥವಾ ಪಡೆಯದಿರಲೂಬಹುದು. ನೀವು ಗುಣಮುಖರಾಗಬಹುದು, ಹಾಗೇಯೇ ಇರಬಹುದು ಅಥವಾ ಇನ್ನೂ ಹೆಚ್ಚಾಗುವ ಸಾಧ್ಯತೆಗಳಿರುತ್ತದೆ. ಒಂದು ವೇಳೆ ನೀವು ಭಾಗವಹಿಸಿದ್ದಲ್ಲಿ, ಇತರೇ ವಯೋವೃದ್ಧ ರೋಗಿಗಳಿಗೆ ಔಷಧಿಯ ಕಾರಣದಿಂದ ಆಗುವ ಸಂಭಾವ್ಯ ಮಾನಸಿಕ ಆರೋಗ್ಯದ ಸಮಸ್ಯೆಗಳ ಬಗ್ಗೆ ಸಾಕ್ಷಿಗಳನ್ನು ಸಂಗ್ರಹಿಸಿಕೊಳ್ಳಲು ಸಹಾಯವಾಗುತ್ತದೆ. ಈ ಮೂಲಕ ವಯೋವೃದ್ಧ ರೋಗಿಗಳಿಗೆ ಸೂಚಿಸಿರುವ ಔಷಧಿಗಳ ಬಗ್ಗೆ ತಿಳುವಳಿಕೆ ಪಡೆಯಬಹುದು.

9.ಯಾವ ಯಾವ ಪರ್ಯಾಯ ಚಿಕಿತ್ಸೆಗಳು ಲಭ್ಯ ಇವೆ?.

ಇದುವರೆಗೆ, ಇದು ಒಂದು ವೀಕ್ಷಣಾ ಅಧ್ಯಯನವಾಗಿದ್ದು, ಇದರಲ್ಲಿ ಯಾವುದೇ ಚಿಕಿತ್ಸೆಯ ಪ್ರಭಾವ ಇರುವುದಿಲ್ಲ.

10. ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗಿಯಾಗುವುದರಿಂದ ತಗಲುವ ವೆಚ್ಚ:

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಗೆ ಪಣ ಪಾವತಿಸಬೇಕಾಗಿಲ್ಲ.

11. ಗಾಯ/ತೊಂದರೆಗೆ ಪರಿಹಾರ.

ಇದು ಒಂದು ವೀಕ್ಷಣಾ ಅಧ್ಯಯನವಾಗಿದ್ದು, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಯಾವುದೇ ರೀತಿಯ ವೈದ್ಯಕೀಯ ತೊಂದರೆಗಳು ಉದ್ಭವಿಸುವುದಿಲ್ಲ.

12. ಮಾಹಿತಿಯ ಗೌಪ್ಯತೆ:

ಈ ಅಧ್ಯಯನದ ಮಾಹಿತಿ ಪ್ರತಿಯಲ್ಲಿ ನಿಮ್ಮ ಹೆಸರು, ವಿಳಾಸ, ವೈದ್ಯಕೀಯ ಸಂಗತಿ, ತಪಾಸಣೆಯ ಫಲಿತಾಂಶಗಳಿರುತ್ತವೆ. ಇವುಗಳನ್ನು ಗೌಪ್ಯವಾಗಿ ಇರಿಸಲಾಗುವುದು. ಈ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಪಟ್ಟ ಸಂಶೋಧಕರು, ಸಂಘದ ನೈತಿಕ ಸಮಿತಿ ಪ್ರಮುಖರು ಅಥವಾ ನಿಯಂತ್ರಕ

ಸಂಸ್ಥೆಯವರು ಪರಿಶೀಲಿಸುವರು ಇದರಲ್ಲಿನ ವೈಯಕ್ತಿಕ ದಾಖಲಾಗಳನ್ನು ನಿಮ್ಮ ಲಿಖಿತ ಅನುಮತಿ ಇಲ್ಲದೇ ಅನ್ಯ ವ್ಯಕ್ತಿಗಳಿಗೆ ನೀಡಲಾಗುವುದಿಲ್ಲ. ಆದರ ಫಲಿತಾಂಶ ಹಾಗು ಮಾಹಿತಿಗಳನ್ನು ನಿಮ್ಮ ವೈಯಕ್ತಿಕ ಗುರುತು, ಹೆಸರು, ವಿಳಾಸಗಳಾವುದನ್ನೂ ತಿಳಿಯಪಡಿಸದೆ ಪ್ರಕಟಿಸಲೂಬಹುದು. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಯಾವುದೇ ರೀತಿಯ ಮೌಖಿಕ ಮತ್ತು ಲಿಖಿತ ಬರವಣಿಗೆಯ ವಿವರಣೆಗಳು ಅವಲಂಬನೆಯಾಗಿರುವುದಿಲ್ಲ.

13.ಅಧ್ಯಯನದ ಬಗ್ಗೆ ಹೊಸ ಮಾಹಿತಿ.

ಈ ಅಧ್ಯಯನದ ಅಭ್ಯಾಸದ ಸಮಯದಲ್ಲಿ ಯಾವುದೇ ಹೊಸ ಮಾಹಿತಿಗಳು ಕಂಡುಬಂದಲ್ಲಿ ಅಭ್ಯಾಸ ಮುಂದುವರಿಸುವ ಬಗ್ಗೆ ನಿಮಗೆ ನಿರ್ಣಯಗಳನ್ನು ತಿಳಿಸಲಾಗುವುದು. ಈ ಅಧ್ಯಯನದ ಫಲಿತಾಂಶಗಳನ್ನು ಪಡೆಯಲು ನೀವು ಇಚ್ಛಿಸಿದಲ್ಲಿ, ಅದನ್ನು ನಿಮಗೆ ನೀಡಲಾಗುತ್ತದೆ.

14. ಐಚ್ಛಿಕವಾಗಿ ಭಾಗವಹಿಸುವಿಕೆ:

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯು ಐಚ್ಛಿಕವಾಗಿದ್ದು, ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಸಮ್ಮತಿಸಿದರೂ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನಿಮ್ಮ ಸಮ್ಮತಿಯನ್ನು ಹಿಂತೆಗೆದುಕೊಳ್ಳಬಹುದು. ಹಾಗು ಇದಕ್ಕೆ ಯಾವುದೇ ಕಾರಣ ನೀಡಬೇಕಾಗಿಲ್ಲ. ಇದಕ್ಕಾಗಿ ನಿಮಗೆ ಯಾವುದೇ ದಂಡವಿಲ್ಲ ಮತ್ತು ಸಿಗಬಹುದಾದ ಪ್ರಯೋಜನ/ನಷ್ಟವಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವ ಮೊದಲು ಹೊರಬಂದರೆ ನಿಮಗೆ ಯಾವುದೇ ಚಿಕಿತ್ಸೆಗೆ ತೊಂದರೆಯಾಗುವುದಿಲ್ಲ. ನಿಮ್ಮ ಮುಂದಿನ ಚಿಕಿತ್ಸೆಯ ಮೇಲೆ ಯಾವ ಅಡ್ಡ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ ಅಥವಾ ನಿಮ್ಮ ವೈದ್ಯರೊಂದಿಗಿನ ಸಂಬಂಧಕ್ಕೆ ಯಾವುದೇ ತೊಂದರೆ ಇರುವುದಿಲ್ಲ.

ಅಧ್ಯಯನ ಪೂರ್ಣಗೊಳಿಸುವ ಮೊದಲು ನೀವು ಹಿಂದೆ ಸರಿದರೆ ನೀವು ಅಧ್ಯಯನದಿಂದ ಹಿಂದೆ ಸರಿಯುವ ಮೊದಲು ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಅಧ್ಯಯನದ ವರದಿಯಲ್ಲಿ ಉಪಯೋಗಿಸಲಾಗುವುದು. ಪ್ರಾಯೋಜಕರು ಅಥವಾ ಅಧ್ಯಯನಕಾರರು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅವರ ಅಧ್ಯಯನವನ್ನು ಅಥವಾ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಒಂದಲ್ಲ ಒಂದು ಕಾರಣಕ್ಕಾಗಿ ನಿಮ್ಮ ಅನುಮತಿ ಇಲ್ಲದೆಯೇ ನಿಲ್ಲಿಸಬಹುದು.

15.ಒಂದು ವೇಳೆ ಪ್ರಶ್ನೆಗಳೇನಾದರೂ ಇದ್ದಲ್ಲಿ, ಯಾರನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು.

ನಿಮಗೆ ಏನಾದರೂ ಪ್ರತಿಕೂಲ ತೊಂದರೆಗಳು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಕಂಡುಬಂದಲ್ಲಿ ಕೂಡಲೇ ಮುಖ್ಯ ಸಂಶೋಧನಾಕಾರ ವೈತಾಲಿ ವಿ. ಶಿಂಧೆ. ಯವರನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು.

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯ ಒಪ್ಪಿಗೆ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನಕಾರರಲ್ಲಿ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳುವ ಹಕ್ಕಿರುತ್ತದೆ. ಹಾಗಿದ್ದಲ್ಲಿ,ನಿಮಗೆ ಸವಸ್ಯ ಕಾರ್ಯದರ್ಶಿಗಳು, ಕಸ್ತೂರ್ಬಾ ಮೆಡಿಕಲ್ ಕಾಲೇಜು, ಮಣಿಪಾಲದ ನೈತಿಕ ಸಮಿತಿ ಸಂಸ್ಥೆಯ ಕೊಠಡಿ ಸಂಖ್ಯೆ 22, ನೆಲಮಹಡಿ, ಕೆ.ಎಮ್.ಸಿ. ಸಿಬ್ಬಂದಿಗಳ ಕೊಠಡಿ, ಕೆ.ಎಮ್.ಸಿ ಆಡಳಿತ ವಿಭಾಗ ಕಛೇರಿಯ ಪಕ್ಕ, ಕಸ್ತೂರ್ಬಾ ಮೆಡಿಕಲ್ ಕಾಲೇಜು, ಮಣಿಪಾಲ-576 104 ಇವರು ವಿವರಗಳನ್ನು ನೀಡುತ್ತಾರೆ.

ದೂರವಾಣಿ ಸಂಖ್ಯೆ: 0820 2933522 ಸಮಯ: 9:00ಬೆಳಿಗ್ಗೆ. 5:00ಸಂಜೆ.

ಈ ಅಧ್ಯಯನದ ಬಗ್ಗೆ ಯಾವುದಾದರೂ ಪ್ರಶ್ನೆ ಅಥವಾ ಸಂಬಂಧಿಸಿದ ವಿಷಯಗಳಿದ್ದಲ್ಲಿ ಈ ಕೆಳಗೆ ತಿಳಿಸಿದ ವ್ಯಕ್ತಿಗಳನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು.

ಹೆಸರು: ಡಾ: ರಾಜೇಶ್ ಪಿ.

ವಿಳಾಸ: ಫಾರ್ಮಸಿ ಪ್ರಾಕ್ಟೀಸ್ ವಿಭಾಗ, ಎಂ ಸಿ ಓ ಪಿ ಎಸ್, ಮಣಿಪಾಲ.

ದೂರವಾಣಿ ಸಂಖ್ಯೆ: +91 9538417313

Appendix III a: Informed Consent Form (English)

INFORMED CONSENT FORM

Project title: Evaluation of antimicrobial agents with potential to develop adverse mental health in geriatrics

I confirm I have read the Participant Information Sheet for the above study and its contents were explained and I have had the opportunity to ask questions and received satisfactory answers.

I understand that my participation in the study is voluntary and that I have the right to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

I agree to take part in the above study. I confirm that I have received a copy of the Participant Information Sheet along with this signed and dated informed consent form.

Name of the Research Participant.:

Age of the Research Participant:

Address of the Research Participant:

Occupation.:

Annual Income of the Participant:

Name & address of the nominee(s) and his relation to the Participant:

_____ _____

Signature of the research subject Date

_____ _____

Name & Signature of the witness Date

_____ _____

Name & Signature of the person explaining the consent Date

Appendix III b: Informed Consent Form (Kannada)

ಮಾಹಿತಿ ಒಪ್ಪಿಗೆ ಪತ್ರ

ಅಧ್ಯಯನದ ಹೆಸರು: ವಯೋವೃದ್ಧರಲ್ಲಿ ಆಂಟಿಮೈಕ್ರೊಬಿಯಲ್ ಔಷಧಿಯಿಂದ ಸಂಭಾವ್ಯ ಪ್ರತಿಕೂಲ ಮಾನಸಿಕ ಆರೋಗ್ಯದ ಬೆಳವಣಿಗೆಯ ಮೌಲ್ಯಮಾಪನ.

ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗೀದಾರರ ಮಾಹಿತಿ ಪತ್ರವನ್ನು ಓದಿ ತಿಳಿದುಕೊಂಡಿರುತ್ತೇನೆ. ಮತ್ತು ಅದರಲ್ಲಿನ ಮಾಹಿತಿಗಳನ್ನು ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ. ನನಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶ ನೀಡಲಾಗಿದ್ದು, ಅವುಗಳಿಗೆ ಸಮಾಧಾನಕರವಾದ ಉತ್ತರಗಳು ಲಭಿಸಿವೆ ಎಂದು ದೃಢೀಕರಿಸುತ್ತೇನೆ.

ಈ ಅಧ್ಯಯನದಲ್ಲಿನನ್ನ ಭಾಗವಹಿಸುವಿಕೆಯು ಐಚ್ಛಿಕವಾಗಿದ್ದು, ನನಗೆ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ, ಯಾವುದೇ ಕಾರಣವಿಲ್ಲದೆ ವೈಯಕ್ತಿಕವಾಗಿ ಭಾಗಹಿಸುವಿಕೆಯಿಂದ ಹಿಂದೆ ಸರಿಯುವ ಹಕ್ಕಿದೆ. ಈ ನಿರ್ಣಯವು ಮುಂದಿನ ವೈದ್ಯಕೀಯ ತಪಾಸಣೆಗೆ, ಕಾನೂನು ಹಕ್ಕಿಗೆ ಯಾವುದೇ ತೊಂದರೆಯಾಗುವುದಿಲ್ಲವೆಂದು ತಿಳಿದಿರುತ್ತೇನೆ.

ನಾನು ಮೇಲೆ ತಿಳಿಸಿದ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಂಡಿದ್ದು ಹಾಗೂ ನಾನು ಸಹಿ ಮಾಡಿದ ಮಾಹಿತಿ ಒಪ್ಪಿಗೆ ಪ್ರತಿಯನ್ನು ಈ ಕೆಳಗಿನ ದಿನಾಂಕದಂದು ಸ್ವೀಕರಿಸಿರುವೆನೆಂದು ದೃಢೀಕರಿಸುತ್ತೇನೆ.

ಭಾಗವಹಿಸುವವರ ಹೆಸರು:

ಭಾಗವಹಿಸುವವರ ವಯಸ್ಸು:

ಭಾಗವಹಿಸುವವರ ವಿಳಾಸ:

ಉದ್ಯೋಗ:

ಭಾಗವಹಿಸುವವರ ವಾರ್ಷಿಕ ಆದಾಯ:

ನೊಮಿನಿಯ(ರ) ಹೆಸರು ಮತ್ತು ವಿಳಾಸ ಮತ್ತು ಭಾಗವಹಿಸುವವರ ಜೊತೆಗೆ ಇರುವ ಸಂಬಂಧ :

_____	_____
ಭಾಗವಹಿಸುವವರ ಸಹಿ	ದಿನಾಂಕ
_____	_____
ಸಾಕ್ಷಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ	ದಿನಾಂಕ
_____	_____
ಒಪ್ಪಿಗೆ ವಿವರಿಸುವ ವ್ಯಕ್ತಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ	ದಿನಾಂಕ

Appendix IV: Case Report Form

CASE REPORT FORM

Sl. NO:

PATIENT DEMOGRAPHICS

Age:	Sex:
Date of admission:	Duration of stay:
Date of discharge:	Occupational Status:

COMPLAINTS ON ADMISSION:
MEDICAL HISTORY:
MEDICATION HISTORY:

Alcoholism	Yes ☐	No ☐	Smoking	Yes ☐	No ☐
Previously administered antimicrobials:	Yes ☐		No ☐		
Co morbidities:		Psychological Problems:			

Final Diagnosis:
Physical Examination: General Examination: HEENT: CVS: RS: EXT: GIT: CNS:
Vital Signs

PR:	BP:	RR:	Temp:

LABORATORY TESTS

Routine Biochemical Investigations			
Urea	TSH	T.Prot	RBC
S.cr	Cortisol	Alb	Hb
Na	T.Ch	Glob	WBC
K	TGs	AST	Platelet
FBS	T.Billi	ALT	ESR
RBS	D.Bili	ALP	HbA1c
PPBS	Amyl	Lipases	BUN

ABG	
pH	
pO_2	
pCO_2	
HCO_3	
O_2 Sat	

Other Tests

X Ray:
ECG:
ECHO:
Sputum Culture:
Urine sample:
Stool sample:
Renal function tests:
Blood Culture:

Duration in ICU	
Days of Hospitalisation	

Treatment Outcome

Improved	Recovered	No Change	Discharged Against Medical Advice	Death
☐	☐	☐	☐	☐

DRUG TREATMENT CHART

DRUG	DOSE	FREQUENCY	DURATION	ADRS

VS

ORIGINALITY REPORT

%14	%5	%9	%5
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Arun Mattappalil, Kari A. Mergenhagen. "Neurotoxicity with Antimicrobials in the Elderly: A Review", Clinical Therapeutics, 2014 Publication	%3
2	Dilip Chandrasekhar, Harsha Manaparambil, Jafer Chalil Parambil. "Outcome assessment of intervention on appropriateness of antibiotic use among geriatric patients: A prospective interventional study from a tertiary care referral hospital", Clinical Epidemiology and Global Health, 2019 Publication	%2
3	pinnacle.allenpress.com Internet Source	%1
4	Cathy Baldwin, Patrick Rawstorne. "Public understanding of risk in health impact assessment: a psychosocial approach", Impact Assessment and Project Appraisal, 2018 Publication	%1
5	Angela Giarratano, Samantha EL Green, David	

	P Nicolau. "Review of antimicrobial use and considerations in the elderly population", Clinical Interventions in Aging, 2018 Publication	%1
6	Submitted to Blackpool and The Fylde College, Lancashire Student Paper	%1
7	www.mdpi.com Internet Source	%1
8	www.archivesofmedicine.com Internet Source	%1
9	"Assessment of Antimicrobial Use Pattern Using World Health Organization Prescribing Indicators at a Tertiary Hospital: A Prospective, Observational study", Journal of Applied Pharmaceutical Science, 2018 Publication	<%1
10	link.springer.com Internet Source	<%1
11	Submitted to Uniformed Services University of the Health Sciences Student Paper	<%1
12	"Posters", Clinical Microbiology and Infection, 2011 Publication	<%1
	Submitted to University of Leeds	

13	Student Paper	<%1
14	"ESCP–GSASA 38th symposium on clinical pharmacy 30 years of clinical pharmacy; a bright future ahead, 3rd–6th November 2009, Geneva, Switzerland", Pharmacy World & Science, 2010 Publication	<%1
15	Submitted to Grand Canyon University Student Paper	<%1
16	JEFFREY J. BORCKARDT, ANOUK L. GRUBAUGH, CHRISTOPHER G. PELIC, CARLA KMETT DANIELSON, SUSAN J. HARDESTY, B. CHRISTOPHER FRUEH. "Enhancing Patient Safety in Psychiatric Settings", Journal of Psychiatric Practice, 2007 Publication	<%1
17	Cone, L.A.. "Delirium in the elderly resulting from azithromycin therapy", Surgical Neurology, 200306 Publication	<%1
18	Submitted to Rochester Institute of Technology Student Paper	<%1
19	hdl.handle.net Internet Source	<%1
20	"The Aging Kidney in Health and Disease", Springer Science and Business Media LLC,	<%1

	2008 Publication	
21	Submitted to UC, Boulder Student Paper	<%1
22	Jino Elsa Thomas, Anil K. Bhat, Mahadev Rao, Vasudeva Guddattu, Sonal Sekhar M. "Use of Vitamin D Supplements in Osteoarthritis: An Observational Study in a Tertiary Health Care Facility", Journal of the American College of Nutrition, 2018 Publication	<%1
23	www.worldagroforestry.org Internet Source	<%1
24	cabi.org Internet Source	<%1
25	worldwidescience.org Internet Source	<%1
26	M. R. Stegemann, C. A. Passmore, J. Sherington, C. J. Lindeman, G. Papp, D. J. Weigel, T. L. Skogerboe. "Antimicrobial Activity and Spectrum of Cefovecin, a New Extended-Spectrum Cephalosporin, against Pathogens Collected from Dogs and Cats in Europe and North America", Antimicrobial Agents and Chemotherapy, 2006 Publication	<%1

27	www.haematologica.org Internet Source	<%1
28	www.hindawi.com Internet Source	<%1
29	Submitted to Manipal University Student Paper	<%1
30	Submitted to University College London Student Paper	<%1
31	Submitted to University of Aberdeen Student Paper	<%1
32	Submitted to Universiti Kebangsaan Malaysia Student Paper	<%1
33	Submitted to Universiti Malaysia Terengganu UMT Student Paper	<%1
34	www.nssc.org Internet Source	<%1

EXCLUDE QUOTES	OFF	EXCLUDE MATCHES	OFF
EXCLUDE BIBLIOGRAPHY	ON		