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Identification of risk factors for hyponatremia in psychiatric patients undergoing treatment: A case control study.

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Identification of Risk factors associated with Hyponatremia in Psychiatric patients undergoing treatment: A Case Control Study

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MANIPAL ACADEMY OF HIGHER EDUCATION

In partial fulfilment for the degree of Doctor of Pharmacy (Pharm D)

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MANIPAL COLLEGE OF PHARMACEUTICAL SCIENCES
MANIPAL
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Certificate

This is to certify that this project report entitled, **"Identification of Risk factors associated with Hyponatremia in Psychiatric patients: A Case Control Study"** by **Ms. Himani Powle, Ms. Ashvitha Shet, Ms. Arline Mendonca** and **Ms. Lakshmi Thulasi** for the completion of 5th year 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. Vijayanarayana K**, M.Pharm, PhD, Associate Professor, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal, **Dr. Girish Thunga**, M.Pharm, PhD, Assistant Professor (Selection Grade) Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education and **Dr. Ravindra Munoli** MBBS, MD (Psychiatry) Assistant Professor, Department of Psychiatry, Kasturba Medical College, Manipal Academy of Higher Education.

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Declaration

We hereby declare that the project entitled **"Identification of Risk factors associated with Hyponatremia in Psychiatric patients: A Case Control Study"** by **Ms. Himani Powle, Ms. Ashvitha Shet, Ms. Arline Mendonca** and **Ms. Lakshmi Thulasi** was carried out under the guidance of **Dr. Vijayanarayana K**, M.Pharm, PhD, Associate Professor, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal. 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.

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LIST OF ABBREVIATIONS

1. SIADH – Syndrome of Inappropriate Antidiuretic Hormone Secretion

2. TCA – Tricyclic Antidepressants

3. SSRI – Selective Serotonin Reuptake Inhibitors

4. CCB – Calcium Channel Blockers

5. ACE – Angiotension Converting Enzyme

6. COPD – Chronic Obstructive Pulmonary Disease

7. CCF – Congestive Cardiac Failure

8. CVA – Cerebrovascular Accident

9. ADH – Anti-Diuretic Hormone

10. ICD – International Classification of Diseases

11. BUN – Blood Urea Nitrogen

12. CNS – Central Nervous System

13. CVS – Cardiovascular System

14. IHD – Ischemic Heart Disease

15. ALD – Alcoholic Liver Disease

16. PTB – Pulmonary Tuberculosis

17. GI – Gastrointestinal

ABSTRACT

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Introduction: Hyponatremia is one of the most common electrolyte imbalance found in psychiatric patients undergoing treatment. Hyponatremia occurs when serum sodium concentration goes below 136 mEq/L and patients with hyponatraemia have increased morbidity and mortality compared to patients without hyponatraemia. Hyponatraemia is often iatrogenic and avoidable, may drugs and co-morbid illness increase the risk of hyponatremia in psychiatric patients. However only few studies are to done to identify the possible risk factors, hence this study was undertaken to identify the risk factors for development hyponatremia in psychiatric patients.

 Methods: A **c**ase-control study was conducted in tertiary care teaching hospital of Southern India. Institutional ethics committee approval was obtained prior to the study. Psychiatric patients admitted between January 2013 to December 2017 were identified from MRD patient files using ICD 10 code F01-F99 and based serum sodium levels, hyponatremia cases (<135 mEq/L) and control (135-145 mEq/L) were selected. Patients information on demographics, medical history, medication history, laboratory parameters, drug treatment, were retrieved from the patient medical records. Risk factors associated with occurrence of hyponatremia were identified by multiple logistic regression and odds ratio (OR) was calculated.

Results: Based on inclusion and exclusion criteria, 264 cases of hyponatremia and 253 control were included in the study. Mean age of hyponatremia patients was 56.4±16.8 years compared to 39.6 ±3.9 years in control. Incidence of hyponatremia was more in males (68.2%). Alcoholism (OR:3.1; 95% CI: 1.8-5.4; p<0.005), history of seizure disorders (OR:10.9; 95% CI: 1.9-63.5; p=0.008), history of PTB (OR:7.4; 95% CI: 1.1-48.1; p=0.036) and metformin (OR:6.8; 95% CI: 1.5-31.5; p=0.008) were identified as independent risk factors for hyponatremia in psychiatric patients by multiple logistic regression. Among comorbidities, hypertension (OR:0.2; 95% CI: 0.1-0.8; p=0.008) and in current medications, atorvastatin (OR= 0.2; 95%CI 0.06-0.7; p=0.021) was found to be a protective factor against hyponatremia.

Conclusion: It was found that alcoholism, history of seizures, PTB and metformin were potential risk factors for hyponatremia in psychiatric patients while hypertension and atorvastatin usage was found to have protective effect against the same.

INTRODUCTION

INTRODUCTION

- **Hyponatremia**

  Hyponatremia is defined as a serum sodium concentration of less than 135 mmol/L[1]. It is the most prevalent electrolyte imbalance encountered in hospitalized patients in both general and psychiatric wards. Hyponatremia is not considered as a disease but rather a physiological process that indicates disturbed water homeostasis. It is a serious health problem associated with morbidity and mortality[2].

- **Classification of hyponatremia**

  Based on the serum sodium concentration, the Joint European guidelines classify hyponatremia in adults as follows[3]:

  > Mild hyponatremia: 130-134 mmol/L
  >
  > Moderate hyponatremia: 125-129 mmol/L
  >
  > Profound hyponatremia: <125 mmol/L

- **Etiology/Risk factors**

  The etiology of hyponatremia is multifactorial. Most of the psychiatric patients present with polydipsia and polyuria. Several factors like Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and hypothalamic defect can also be a reason for hyponatremia[4]. Due to lack of understanding about the incidence, presentation and risk factors of psychotropic-induced hyponatremia, physicians often overlook hyponatremia[2].

  High risk factors for hyponatremia include extreme old age of greater than 80 years, low body weight, female gender, history of hyponatremia/low baseline sodium concentration, longer psychiatric illness duration, co-therapy with drugs known to be associated with causing hyponatremia which includes diuretics, Tricyclic Antidepressants (TCA), Selective Serotonin Reuptake inhibitors (SSRI), Calcium Channel Blockers (CCB), Angiotensin Converting Enzyme (ACE) inhibitors, cancer chemotherapy and Carbamazepine, deteriorated renal function, medical comorbidities like hypothyroidism, diabetes, Chronic Obstructive Pulmonary Disease (COPD), Hypertension (HTN), Congestive Cardiac failure (CCF), Cerebrovascular Accident (CVA), liver cirrhosis, various cancers and head injuries, alcoholics, malnourished patients, hypokalemic patients, burn patients[1,2].

- **Epidemiology**

Hyponatremia accounts for 10.5% of the psychiatric cases[5]. The studies indicate that the prevalence of polydipsia in chronically ill psychiatric patients ranges from 6% to 17% and one half of the psychiatric patients with polydipsia will go on to have symptoms of water intoxication. Among psychiatric patients with polydipsia, 69%-83% are schizophrenics. The prevalence of polydipsia is slightly higher in women i.e. 60%-80%[4].

- **Pathogenesis of hyponatremia:**

1. **Psychogenic Polydipsia**:
   Inability of the kidneys to excrete a water load or excessive water intake leads to hyponatremia. Intake of water depends on the thirst mechanism. The increase in osmolality stimulates thirst which is sensed by the osmoreceptors that are located in the hypothalamus leading to the release of vasopressin from the posterior pituitary. Vasopressin acts on the Vasopressin 2 (V2) receptors of the collecting duct cells and leads to increased aquaporin expression on the collecting duct cells, thus increasing water absorption and abolishes thirst[6].

2. **Syndrome of Inappropriate Antidiuretic Hormone Secretion:**
   Hyponatremia caused by SIADH is due to the increased release of Anti Diuretic Hormone (ADH).
   ADH is inappropriately elevated by a variety of mechanisms including:
   - Enhanced and unregulated secretion of ADH by tumor or hypothalamus.
   - Increased ADH secretion in basal state and in response to hypertonicity.
   - Reset osmostat i.e. serum osmolality lower than normal below which the secretion of ADH is suppressed.
   - V2 receptor mutation activation permitting reabsorption of water in the absence of ADH[6].

3. **Beer drinkers potomania:**

   Alcohol abuse is very common in psychiatric patients and often present with hyponatremia. As the solute intake is inadequate, the patients often have reduced ability to excrete free water and develop hyponatremia with low urine osmolality[7].

● **Signs and symptoms**

- Mental status disturbances like confusion, disorientation, restlessness, irritability and psychosis.
- Neurological disturbances like headache, blurred vision, seizures, stupor and coma.
- Gastrointestinal disturbances like nausea, vomiting and diarrhea.
- Musculoskeletal disturbances like muscle cramps, twitches, tremors.
  Water seeking and excessive water drinking behavior is seen in polydipsic patients[8].

● **Complications**

1. Chronic hyponatremia can lead to decreased bone mineral density with increasing bone fragility[9].
2. An acute onset of severe hyponatremia can cause cerebral edema leading to fatal herniation[10].
3. Osmotic demyelination syndrome, a neurological condition can occur from rapid correction of chronic hyponatremia[11].
4. Hyponatremia can induce stress cardiomyopathy due to psychogenic polydipsia[12].
5. Premenopausal women are at a greater risk of hyponatremia-related brain damage which may be related to the effects of women's sex hormones on the body's ability to balance sodium levels[13].

● **Mortality**

According to the results of a meta regression analysis which included all English language published studies until 2014 that compared the mortality rate in patients with or without improvement of hyponatremia, it was found that the patients in whom sodium concentration was improved - the overall mortality rate was reduced by up to 60% compared to the patients in whom there was no improvement in their hyponatremia[14].

Profound hyponatremia has a high mortality rate. In patients whose serum sodium concentration goes below 105 mmol/L, and especially in alcoholics, the mortality is greater than 50%[15].

NEED FOR THE STUDY

NEED FOR THE STUDY

- **Need**: Hyponatremia is a prevalent and potentially dangerous comorbidity in psychiatric patients and accounts for 10.5% of the cases. Among psychiatric patients, hyponatremia is believed to be frequently underdiagnosed because clinical signs may mimic psychopathological symptoms of the underlying condition. Hyponatremia can lead to severe complications such as cerebral edema, brain disease, herniation of the brain, cardiopulmonary arrest, seizure, coma and even death. It is crucial to treat hyponatremia before it hinders the treatment of psychiatric inpatients. This study emphasizes on identification of all possible risk factors associated with hyponatremia in psychiatric patients rather than focusing on a single risk factor or mental disorder giving the physician a better insight on prioritizing the management.

  Our study analyses individual drug association as compared to the study carried out by Seigler et. al which analyzed only the class of drugs associated to causing hyponatremia[18]. In the previous study renal diseases were confirmed to be the strongest risk factor associated to hyponatremia in psychiatric patients. So in this study, the exclusion criteria was patients with renal diseases which gives us an edge to find more risk factors other than the well-established ones.

  Recent studies also reveal the association of hyponatremia to vitamin D which is responsible for certain behavioral and gait disturbances. This study also analyses the vitamin D and calcium levels of the psychiatric patients.

- **Impact**: Prompt recognition and optimal management of hyponatremia in hospitalized patients may help achieve the following:

  - Reduce in-hospital mortality and symptom severity allow for less intensive hospital care, decrease the duration of hospitalization and associated costs.
  - It will help the physician establish a relationship between the severity of hyponatremia and comorbid conditions and hence devise a better treatment plan for the same preventing future complications.
  - Identify and modify drug-related risk factors for hyponatremia.
  - Monitor response to therapy by determining alternative hyponatremia treatment options.
  - Help assess chronicity of hyponatremia before recommending treatment.
  - Aggressively monitor hyponatremia treatment to avoid overcorrection.
  - Improve the treatment of underlying comorbid conditions and patients' quality of life.

OBJECTIVES

OBJECTIVES

- **General objective:**

  Identification of risk factors associated with hyponatremia in psychiatric patients.

- **Specific objective:**

  - ✓ To know the prevalence and extent of hyponatremia in patients with psychiatric illness
  - ✓ To know the socio-demographic characteristics of hyponatremia in patients with psychiatric illness
  - ✓ To know the types of co-morbid conditions present in hyponatremia patients with psychiatric illness
  - ✓ To know the past and present medication history of hyponatremia patients with psychiatric illness
  - ✓ To identify the risk factors associated with hyponatremia in patients with psychiatric illness using multiple logistic regression

METHODOLOGY

METHODOLOGY

- **Study Site**: Kasturba Hospital, Manipal.

- **Study Design**: Case-Control Study (January 2013-December 2017)

- **Study Period**: 12 months

- **Ethical Clearance**: Obtained from the Institutional Ethics Committee, Kasturba Hospital, Manipal MAHE. (Letter of approval in Appendix 1).

- **Sample Size**: Absolute precision method was used for calculation of sample size. From the pilot study, expected rate of hyponatremia in psychiatric patients was approximately 15% and margin of error in estimating the hyponatremia (precision) was fixed at 5.0% with 95% confidence level.

$$n = \frac{Z_\alpha^2 \ P \ (1-P)}{d^2} = \frac{1.96^2 \ x \ 0.15 \ (1-0.15)}{0.05^2} = 195.92$$

A total number of 800 subjects diagnosed with psychiatric illness during the period of January 2013 to December 2017 were included in the study. Among them 264 deemed cases of hyponatremia were confirmed based only on recorded serum sodium levels and 253 patients without hyponatremia were considered as controls.
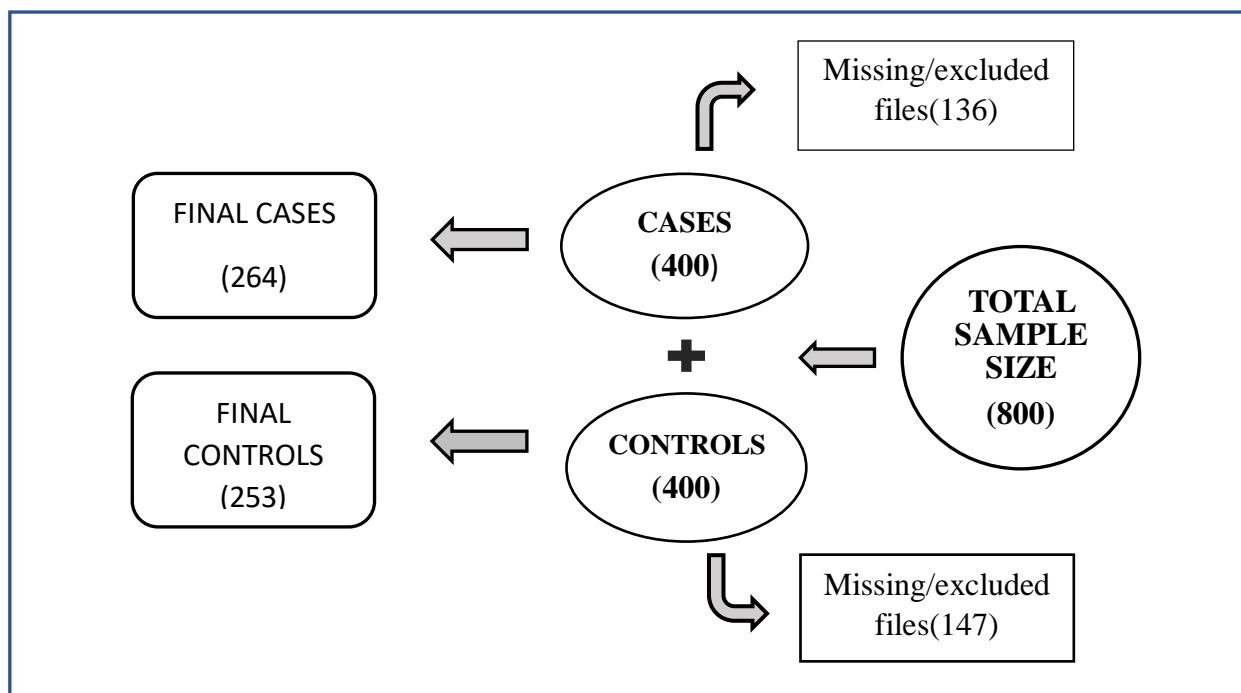
Figure 1: Calculation of Sample Size

- **Study Criteria:**

  Cases: Psychiatric patients with serum sodium levels of less than 135 mEq/L.
  Controls: Psychiatric patients with serum sodium levels between 135-145 mEq/L.

  Inclusion Criteria: Cases: All psychiatric patients with serum sodium levels of less than 135 mEq/L.

  Controls: All psychiatric patients with serum sodium levels between 135-145 mEq/L.

  Exclusion Criteria: 1. Psychiatric patients in whom serum sodium levels were not checked.

  2. Psychiatric patients in whom the serum sodium levels were >145 mEq/L.

  3. Patients with renal disease.

- **Sources for Data Collection:** Patient Case Records.

- **Materials Used**: Case Record Form (CRF). (Appendix 2)

- **Identification of Patient**: The patients were identified from Medical Records Department using ICD 10 code F01-F99 belonging to class Mental, Behavioral and Neurodevelopmental disorders. Data was collected from patients' medical records.

- **Collection of Data:**

  Psychiatric patients were identified from Medical Records Department using ICD 10 code F01-F99 belonging to class Mental, Behavioural and Neurodevelopmental disorders who were admitted to Kasturba Hospital, Manipal, over a 5-year period (January 2013-December 2017), for laboratory evidence of hyponatremia. Those patient records where all serum sodium values during hospital stay were less than 135 mmol/L were considered as cases and those between 135 mmol/L to 145mmol/L were selected as controls. From each selected patient file, demographic information and clinical data, basic laboratory tests, social history, family history, medication history, type and duration of psychiatric illness, comorbidities and drugs prescribed were collected and entered in case record forms (CRF).

8

- **Analysis of data:**

Continuous data was expressed as Mean ± SD. Nominal data was described and expressed in frequency and percentage. Unpaired t-test was used to compare the statistical significance of continuous variables between cases and controls. Univariate analysis was used to identify the risk factors associated with hyponatremia in psychiatric patients and calculation of unadjusted odds ratio. Odds ratio is a measure of the association between risk factors and outcome (hyponatremia). The factors identified in univariate analysis with $p < 0.25$ were selected and taken for multiple logistic regression for calculation of p value and adjusted odds ratio. Data entry and statistical analysis were done using IBM SPSS software version 20.0.

RESULTS

RESULTS

A total of 800 patient records were identified with a confirmed diagnosis of psychiatric illness over a period of 5 years from January 2013 – December 2017 in Kasturba Hospital, Manipal. Among them 264 deemed cases of hyponatremia were confirmed based only on recorded serum sodium levels and 253 patients without hyponatremia were considered as controls. 283 cases were not considered either due to exclusion criteria or missing records. Among the cases, occurrence of moderate hyponatremia was highest (n = 119, 45.2%) followed by profound hyponatremia (n = 78, 29.7%) and mild hyponatremia (n = 66, 25.1%)

I. **Demographic, Social and Biochemical Characteristics:**

The demographic, social and biochemical characteristics of the study population are described in **Table 1.** The mean age of the hyponatremia population was 56.4 ± 16.78 years as compared to 39.58 ± 13.99 years in controls. A majority of patients who were of >60 years of age accounted for maximum number of cases (n = 120, 81.6%). The study population comprised of higher population of males (n = 340, 65.7%) as compared to females. Hyponatremia was found to be dominant in males (n = 180, 52.9%) than females (n = 84, 47.45%)

Significant alcoholic history was observed in the study population (n = 141, 27.2%) and made up 65.24% of the cases. Compared to the controls, 78.57 % of cases constituted tobacco chewers.

About 107 (20.7%) patients were found to have history of psychiatric illness in the family. The proportion of psychiatric family history in cases is depicted in **Figure 2.**

The biochemical characteristics of the study population are described in **Table 2.** Vitamin D was found to be significantly low in cases (19.87 ± 12.9). On the other hand, serum creatinine, serum potassium and BUN were found to be significantly high in the cases with a mean ± SD of 1.0 ± 0.77, 4.28 ± 0.82 and 12.07 ± 10.13 respectively.

Table 1: Demographic and other characteristics of study population

Parameter	Total (n = 517)	Cases (n = 264)	Control (n = 253)
Age (mean ± SD)	48.19 ± 17.62	56.4 ± 16.78	39.58 ± 13.99
Age category			
• <60, n (%)	370 (71.5%)	144 (38.95%)	226 (61.08%)
• >=60, n (%)	147 (28.4%)	120 (81.6%)	27 (18.3%)
Gender, n (%)			
• Males, n (%)	340 (65.7%)	180 (52.9%)	160 (47.05%)
• Females, n (%)	177 (34.2%)	84 (47.45%)	93 (52.54%)
Smoking , n (%)	61 (11.7%)	30 (49.18%)	31 (50.81%)
Alcoholism , n (%)	141 (27.2%)	92 (65.24%)	49 (34.75%)
Tobacco chewer, n (%)	14 (2.7%)	11 (78.57%)	3 (21.42%)
Serum Sodium (mean ± SD)	132.44 ± 8.22	125.85 ± 6.23	139.32 ± 2.28
Hyponatremia category, n(%)			
• Mild	66 (25.1%)		
• Moderate	119 (45.2%)		
• Severe	78 (29.7%)		
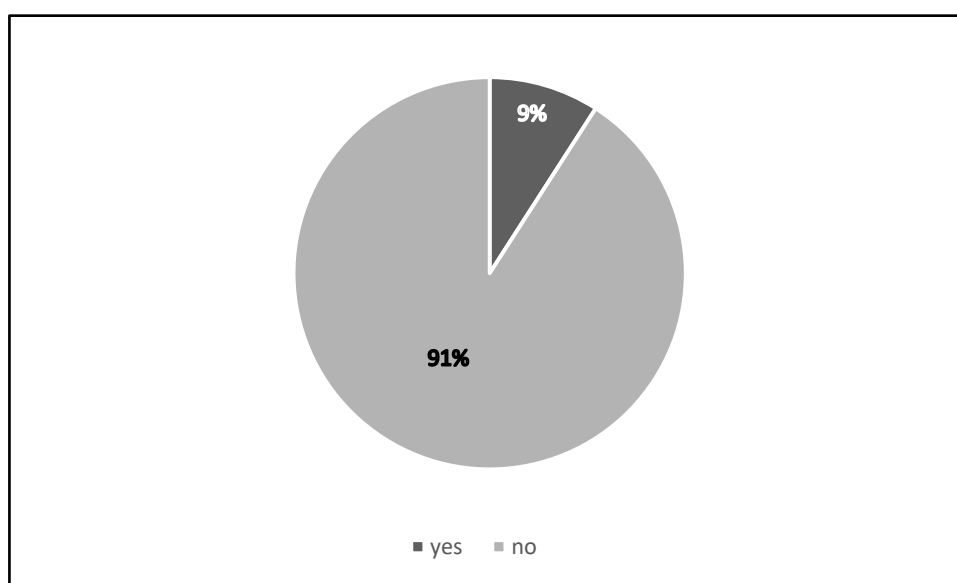
Figure 2: Psychiatric Family history in study population

Table 2: Biochemical Characteristics of study population

Laboratory Parameters	Total (n = 517)	Cases (n = 264)	Control (n = 253)	P value
• **Serum Calcium**	8.89 ± 0.81	8.75 ± 0.77	9.32 ± 0.79	0.869
• **Calcium Category:**				
Low	34 (6.5%)	29 (85.29%)	5 (14.7%)	
Normal	33 (6.3%)	22 (66.6%)	11 (33.3%)	
High	3 (0.5%)	2(66.6%)	1 (33.3%)	
• **Vitamin D**	23.73 ± 17.23	19.87 ± 12.91	30.18 ± 21.82	0.007
• **Vitamin D Category:**				
Deficiency	20 (3.8%)	14 (70%)	6 (30%)	
Normal	12 (2.3%)	6 (50%)	6 (50%)	
• **Serum potassium**	4.2 ± 0.67	4.28 ± 0.82	4.12 ± 0.44	<0.0005
• **Potassium Category:**				
Low	43 (8.3%)	28 (65.1%)	15 (34.8%)	
Normal	416 (80.4%)	190 (45.6%)	226 (54.3%)	
High	46 (8.8%)	39 (84.7%)	7 (15.2%)	
• **Serum creatinine**	0.93 ± 0.62	1.0 ± 0.77	0.87 ± 0.41	0.001
• **Creatinine Category:**				
Low	7 (1.3%)	5 (71.4%)	2 (28.5%)	
Normal	424 (82%)	204 (48.1%)	220 (51.8%)	
High	54 10.4%)	41 (75.9%)	13 (24%)	
• **BUN**	10.8 ± 8.09	12.07 ± 10.13	9.41 ± 4.59	P<0.0005
• **BUN Category:**				
Low	125 (24.1%)	64 (51.2%)	61 (48.8%)	
Normal	317 (61.3%)	156 (49.2%)	161 (50.7%)	
High	38 (7.3%)	31 (81.5%)	7 (18.4%)	

II.   Medical History/Comorbidities/ Psychiatric illness in study population:

The medical history of the study population is described in **Table 3**. Seizure disorder was found to be highest among the cases (91.3%) followed by IHD (90%), pulmonary tuberculosis (88.2%), CVA (87.5%) and hypertension (73.1%) as compared to controls.

The comorbidities of the study population are described in **Table 4.** SIADH (90%) was the most common comorbidity with highest incidence of hyponatremia followed by pneumonia (88.8%), CVA (83.3%), COPD (83.3%) and pulmonary tuberculosis (83.3%).

The percentage distribution of psychiatric illness in study population is depicted in **Figure 3.** ADS Alcohol Dependence Syndrome accounted for maximum number of cases followed by depression, dementia and delirium.

Disease	Total (n = 517)	Cases (n = 264)	Control (n = 253)
Hypertension	123 (23.7%)	90 (73.1%)	33 (26.8%)
IHD	20 (3.8%)	18 (90%)	2 (10%)
CVA	16 (3.0%)	14 (87.5%)	2 (12.5%)
SEIZURES	23 (4.4%)	21 (91.3%)	2 (8.69)
Type 2 diabetes mellitus	90 (17.4%)	62 (68.8%)	28 (31.1%)
Hepatic disorder	20 (3.8%)	13 (65%)	7 (35%)
GI disorder	17 (3.2%)	11 (64.7%)	6 (34.2%)
PTB	17 (3.2%)	15 (88.2%)	2 (11.7%)

Table 3: Medical history of the study population

Table 4: Co-morbidities in study population

Co-morbidity	Total (n = 517)	Cases (n = 264)	Control (n = 253)
CNS			
• Seizures	33 (6.3)	27 (81.8%)	6 (18.1%)
• CVA	12 (2.3%)	10 (83.3%)	2 (16.6%)
CVS			
• Hypertension	103 (19.9)	66 (64%)	37 (35.9%)
Endocrine			
• Diabetes mellitus	83 (16%)	54 (65%)	29 (34.9%)
• SIADH	11 (2.1%)	10 (90%)	1 (9.09%)
Hepatic			
• Cirrhosis	16 (3%)	13 (81.2%)	3 (18.7%)
• ALD	18 (3.4%)	11 (61.1%)	7 (38.8%)
Orthopedic*	22 (4.2%)	12 (54.5%)	10 (45.4%)
Pulmonary			
• Pneumonia	18 (3.4%)	16 (88.8%)	2 (11.1%)
• COPD	12 (2.3%)	10 (83.3%)	2 (16.6%)
• PTB	18 (3.4%)	15 (83.3%)	3 (16.6%)
Gastrointestinal	49 (9.4%)	41 (83.6%)	8 (16.3%)

(* - fractures, spondylitis, herniated disc)
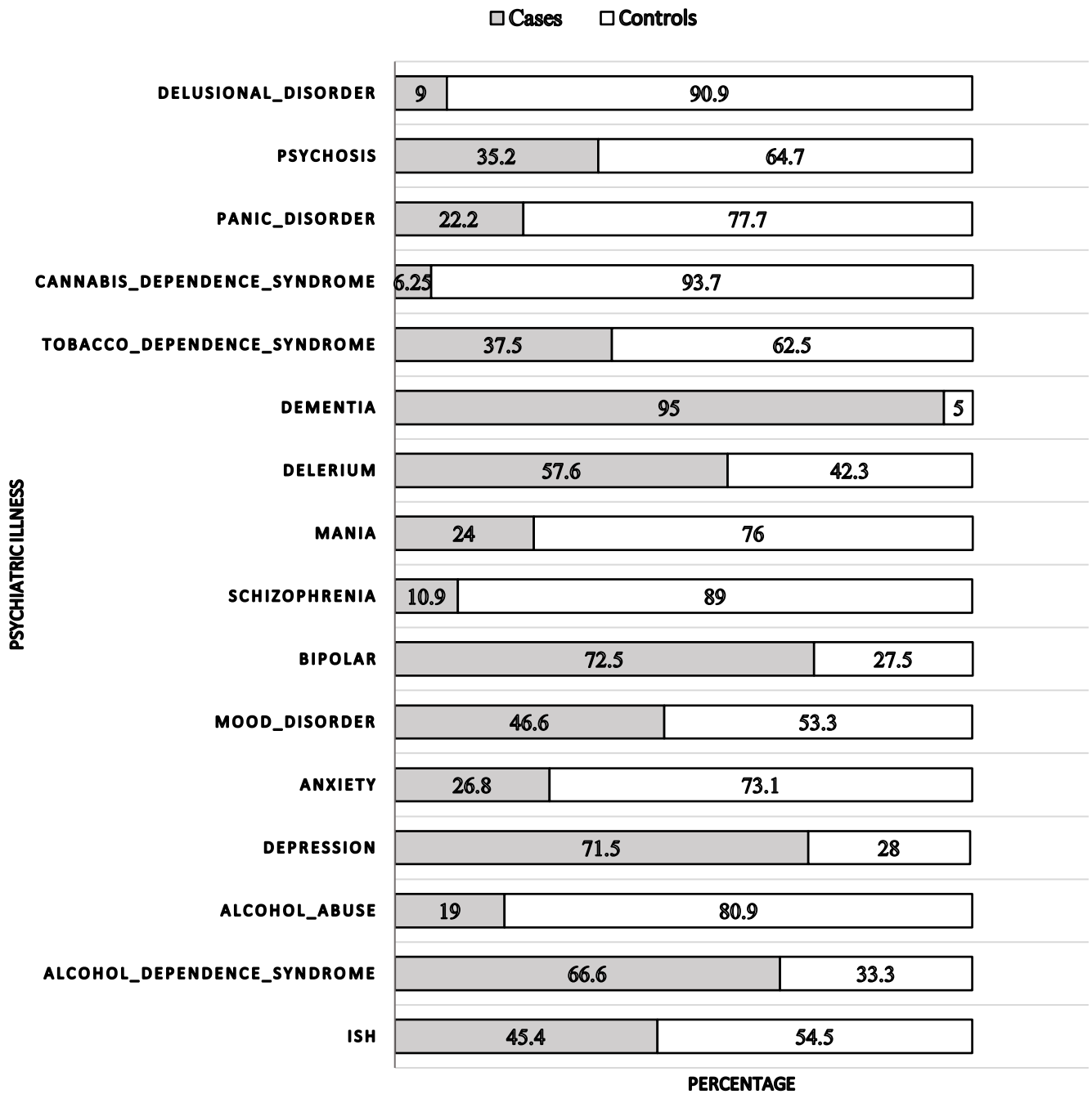
Figure 3: Distribution of Psychiatric Illness in study population

III. Medication History/ Current Medications in study population:

The data about past medication history has been described in **Table 5**. The descriptive analysis of past medications suggested maximum use of anti-alzheimer's drugs among the cases i.e. (90.9%) followed by metformin (85.7%) and lorazepam (80%) as compared to controls.

The data about current medication history has been described in **Table 6.** Compared to controls, furosemide (94.4%) was the most prescribed drug in the cases followed by donepezil (94.1%), levodopa-carbidopa (93.3%) and memantine (88.8%),

Table 5: Past Medications used in study population

Medications	Total (n = 517)	Cases (n = 264)	Control (n = 253)
Quetiapine	24 (4.6%)	13 (54.1%)	11 (43.8%)
Escitalopram	17 (3.2%)	10 (58.8%)	7 (41.1%)
Lorazepam	15 (2.9%)	12 (80%)	3 (20%)
Anti-parkinson's*	20 (3.8%)	12 (60%)	8 (40%)
Anti-alzheimer's **	11 (2.1%)	10 (90.9%)	1 (9.09%)
Carbamazepine	10 (1.9%)	6 (60%)	4 (40%)
Anti-hypertensives			
• Amlodipine	21 (4%)	16 (76.1%)	5 (23.8%)
• Telmisartan	13 (2.5%)	10 (76.9%)	3 (23.07%)
Metformin	21 (4%)	18 (85.7%)	3 (14.2%)

(* - antiparkinson's drugs like levodopa-carbidopa, trihexyphenidyl, ropinirole)

(** - antialzheimer's drugs like memantine, donepezil, amantadine)

Table 6: Current Medications used in study population

Medications	Total (n = 517)	Cases (n = 264)	Controls (n = 253)
Quetiapine	120 (23.2%)	80 (66.6%)	40 (33..3%)
Haloperidol	83 (16%)	47 (56.6%	36 (43.3)
Furosemide	37 (7.1%)	35 (94.5%)	2 (5.4%)
Spironolactone	14 (2.7%)	12 (85.7%	2 (14.2%)
Phenytoin	15 (2.9%)	11 (73.3%)	4 (26.6%)
Levetiracetam	38 (7.3%)	28 (73.6%)	10 (26.3%)
Losartan	10 (1.9%)	7 (70%)	3 (30%)
Telmisartan	13 (2.5%)	7 (53.8%)	6 (46.1%)
Metaprolol	19 (3.6%)	14 (73.6%)	5 (26.3%)
(Amlodipine	68 (13.1%)	41 (60.2%)	27 (39.7%)
Glimepiride	21 (4%)	12 (57.1%)	9 (42.8%)
Insulin	27 (5.2%)	22(81.4%)	5 (8.5%)
Atorvastatin	25 (4.8%)	16 (64%)	9 (36%)
levodopa_carbidopa	15 (2.9%)	14(93.3%)	1 (6.6%)
Memantine	9 (1.7%)	8 (88.8%)	1 (11.1%)
Donepezil	17 (3.2%)	16 (94.1%)	1 (5.8%)
Acamprosate	23 (4.4%)	12 (52.1%)	11 (47.8%)

IV. Identification of risk factors for hyponatremia by Univariate analysis:

The factors having significant association with hyponatremia are mentioned with their odds ratio and *p* value in **Table 7.**

Table 7: Results of Univariate analysis of risk factors for hyponatremia

Factors	Odds ratio	95% CI	*p* value
Age	1.069	1.055 - 1.083	<0.0005
Alcoholism	2.227	1.49 - 3.328	<0.0005
Tobacco chewer	3.623	0.999 - 13.143	0.05
Medical history			
CVS	3.979	2.606 - 6.074	<0.0005
• Hypertension	3.448	2.208 - 5.385	<0.0005
• IHD	9.183	2.108 - 39.995	0.003
CNS	3.23	1.717 - 6.075	<0.0005
• CVA	7.028	1.581 - 31.243	0.01
• Seizures	10.846	2.516 - 46.752	0.001
Endocrine	1.561	1.024 - 2.381	0.039
• T2DM	2.466	1.519 - 4.006	<0.0005
Hepatic	1.82	0.714 - 4.639	0.21
Pulmonary	2.61	1.27 - 5.363	0.009
• PTB	7.56	1.711 - 33.404	0.008
Infectious	3.486	1.132 - 10.737	0.03
Medication history			
• Lorazepam	3.968	1.106 - 14.232	0.034
• Anti-alzheimer's	9.921	1.261 - 78.076	0.029
• Amlodipine	3.2	1.154 - 8.87	0.025
• Telmisartan	3.281	0.892 - 12.062	0.074
• Metformin	6.098	1.774 - 20.963	0.004
Comorbidities			
• Seizures	4.69	1.902 - 11.563	0.001
• Hypertension	1.946	1.245 - 3.041	0.003
• CVA	4.941	1.072 - 22.776	0.04

• T2DM	1.986	1.218 - 3.239	0.006
• SIADH	9.921	1.261 - 78.076	0.029
• Cirrhosis	4.316	1.215 - 15.331	0.024
• Pneumonia	8.097	1.842 - 35.583	0.006
• COPD	4.941	1.072 - 22.776	0.04
• PTB	5.02	1.435 - 17.556	0.012
Current medications			
• Quetiapine	2.315	1.509 - 3.551	<0.0005
• Furosemide	19.181	4.562 - 80.648	<0.0005
• Spironolactone	5.976	1.324 - 26.975	0.02
• Phenytoin	2.707	0.85 - 8.614	0.092
• Levetiracetam	2.883	1.37 - 6.066	0.005
• Losartan	2.27	0.58 - 8.876	0.239
• Metoprolol	2.778	0.986 - 7.828	0.053
• Amlodipine	1.539	0.915 - 2.588	0.104
• Insulin	4.509	1.68 - 12.099	0.003
• Atorvastatin	1.749	0.758 - 4.034	0.19
• Levodopa-carbidopa	14.112	1.842 - 108.127	0.011
• Donepezil	16.258	2.14 - 123.528	0.007

V. **Identification of risk factors for hyponatremia by Multiple Logistic Regression**:

The factors identified in univariate analysis with a minimum of at least 10 events and $p < 0.25$ were selected and taken for multiple logistic regression. The result of multiple logistic regression along with the adjusted OR, 95% CI and *p* value is presented in **Table 8.**

The association remained intact only with certain variables and rest may have failed to show higher intensity of the association to odds ratio due to the presence of confounding factors.

a) **Medical/Medication history and risk of Hyponatremia:**

Patients with history of seizure disorders (Adjusted OR=10.968; 95% CI 1.895-63.479) followed by pulmonary tuberculosis (Adjusted OR =7.404; 95% CI 1.139-48.124) showed higher magnitude of associated odds ratio being one of the leading risk factors causing Hyponatremia.

Medication history of metformin (Adjusted OR = 6.846; 95% CI 1.488-31.488) was associated with risk of causing hyponatremia.

b) **Co-morbidities and risk of Hyponatremia:**

Hypertension. (OR 0.266; 95% CI 0.101-0.702) was found to be a protective factor against hyponatremia.

c) **Current Medications prescribed and risk of Hyponatremia.:**

Although the univariate analysis showed association of drugs like quetiapine, diuretics (furosemide and spironolactone), anti-epileptic drugs like phenytoin and levetiracetam, only atorvastatin (OR= 0.2; 95%CI 0.06-0.7) was found to have statistical significance but as a protective factor for hyponatremia.

Table 8: Multivariate analysis of risk factors for hyponatremia

Factors	Odds ratio	95 % CI	*p* value
Age	1.072	1.052 - 1.093	<0.0005
Alcoholism	3.094	1.779 - 5.381	<0.0005
Tobacco chewer	2.614	0.589 - 11.602	0.206
Medical history			
• Hypertension	2.149	0.859 - 5.376	0.102
• IHD	4.076	0.64 - 25.939	0.137
• CVA	6.365	0.586 - 69.154	0.128
• Seizure	10.968	1.895 - 63.479	0.008
• PTB	11.404	1.139 - 48.124	0.036
Medication history			
• Lorazepam	4.326	0.945 - 19.791	0.059
• Metformin	6.846	1.488 - 31.488	0.013
Comorbidities			
• Seizures	2.516	0.632 - 10.008	0.19
• Hypertension	0.266	0.101 - 0.702	0.008
• Pneumonia	3.56	0.611 - 20.745	0.158
Current Medications			
• Quetiapine	1.549	0.869 - 2.764	0.138
• Amlodipine	0.533	0.226 - 1.255	0.15
• Atorvastatin	0.218	0.06 - 0.792	0.021
• Donepezil	5.697	0.579 - 56.062	0.136

DISCUSSION

DISCUSSION

Hyponatremia is a prevalent and potentially dangerous comorbidity in psychiatric patients and accounts for 15% of the cases. Among psychiatric patients, hyponatremia is believed to be frequently underdiagnosed because clinical signs may mimic psychopathological symptoms of the underlying condition.

From multiple logistic regression, age was found to be a mild factor for causing hyponatremia. Hawkins RC et al. stated that progressing age has been considered as a strong risk factor for causing both hypo- and hypernatremia[16]. Tolouian R et al. stated that the elderly population has a higher risk of bone fractures, impaired attention and falls due to asymptomatic hyponatremia which can be dangerous. Thus, inorder to reduce the morbidity and mortality, correction of hyponatremia is of utmost importance[17]. However, a study by Seigler EL et al. showed that age also seems to be strongly confounded by drugs and comorbidities which usually are present in the older age and might be responsible for the hyponatremia[18].

From the univariate analysis it was found that males were more prone to develop hyponatremia than females.

Alcoholism was assessed to be a potential risk factor for hyponatremia in the study population. (Adjusted OR = 3.094; 95% CI 1.779 - 5.381). Liamis GL et al. stated that decreased sodium levels in hyponatremia was found as the third most electrolyte abnormality in alcoholics(17.3%)[19]. Another study by Michal O et al. showed that the quality of life of alcoholic people, both psychological and psychical, has been found to be worsened due to hyponatremia as compared to the healthy counterparts[20].

Seizures history (Adjusted OR = 10.846; 95% CI = 2.516 - 46.752) as well as concurrent Seizure disorder have been shown to have a significant correlation to hyponatremia. A study by Siegel AJ et al. reported that concurrent usage of duloxetine and hydrochlorothiazide caused SIADH and sodium

depletion respectively, which further resulted in life threatening hyponatremic encephalopathy with seizures[21].

Pulmonary TB (Adjusted OR = 7.404; 95% CI 1.139 - 48.124) was concluded to be a risk factor for hyponatremia from the regression analysis. Lee P et al. stated that patients with pulmonary disorders are known to have SIADH as one of the leading causes of hyponatremia with ectopic ADH secretion as one of the probable mechanisms[22]. Jafari NJ et al. suggested that elderly patients with PTB are at an increased risk of developing hyponatremia[23].

Hypertension, amlodipine and atorvastatin were found to be statistically significant but protective factors for hyponatremia in psychiatric patients of study population.

Vitamin D was found to be significantly low in cases (19.87 ± 12.9). On the other hand, serum creatinine, serum potassium and BUN were found to be significantly high in the cases.

LIMITATIONS

<u>LIMITATIONS</u>

1. The patient population was a mixture of both patients with specific Psychiatric illness and general patient population with secondary consultation for Psychiatric illness.

2. The medication histories depend on the adherence pattern of the patient which was not taken into consideration.

3. There might have been information bias

4. The failure of obvious drugs known to cause Hyponatremia like Diuretics to remain statistically significant in the multivariate logistic regression analysis could be due to small number of subjects who used these drugs.

CONCLUSION

CONCLUSION

- Hyponatremia is a prevalent and potentially dangerous comorbidity in psychiatric patients and accounts for 10.5% of the cases. Among psychiatric patients, hyponatremia is believed to be frequently underdiagnosed because clinical signs may mimic psychopathological symptoms of the underlying condition. The risk factors identified for hyponatremia included male population, alcoholic and tobacco intake history amongst the demographics and serum potassium, serum creatinine, BUN and vitamin D amongst the laboratory parameters. Age, although found to be significant, cannot be considered as a potential risk factor due to probability of confounding due to drugs and comorbidities. Medical history of PTB, seizures and medication history of metformin were concluded to be potential risk factors. Comorbidity of hypertension and current usage of atorvastatin were found to have protective action against hyponatremia in psychiatric patients.

- Prompt recognition, identification of risk factors and optimal management of hyponatremia in hospitalized patients would
    - ✓ Reduce in-hospital mortality and symptom severity allow for less intensive hospital care, decrease the duration of hospitalization and associated costs.
    - ✓ It will help the physician establish a relationship between the severity of hyponatremia and comorbid conditions and hence devise a better treatment plan for the same preventing future complications.
    - ✓ Identify drug-related risk factors for hyponatremia and modify as needed.
    - ✓ Develop a model/tool to identify and evaluate the risk factors for use in a clinical setting.
    - ✓ Determine alternative hyponatremia treatment options and monitor response to therapy.
    - ✓ Help assess chronicity of hyponatremia before recommending treatment.
    - ✓ Aggressively monitor hyponatremia treatment to avoid overcorrection.
    - ✓ Improve the treatment of underlying comorbid conditions and patients' quality of life.

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APPENDICES

Appendix - I

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 11th July 2018   **IEC : 415/2018**

Project title	:	Identification of risk factors for hyponatremia in psychiatric patients undergoing treatment: A case control study.
Principal Investigator	:	Miss. Ashvitha Shet
Guide/ Co Guide/ Co Investigators	:	Himani Powle, Arline Mendonca, Lakshmi Thulasi, Dr. Vijaynarayana K, Dr. Girish Thunga, Dr. Ravindra Munoli
Name & Address of Institution	:	Department of Pharmacy Practice, MCOPS, Manipal. Department of Psychiatry, KMC, Manipal.
Status of review	:	New
Date of review	:	10.07.2018
Decision of the IEC	:	Approved for the study period from 10.07.2018 to 09.07.2019 as mentioned in protocol.

- 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.

Dr. Stanley Mathew
MEMBER SECRETARY - IEC

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)

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Appendix – II

CASE RECORD FORM

Title: "Identification of risk factors for hyponatremia in psychiatric patients undergoing treatment: A Case Control study"

UIN: Height: BMI:			Date of Admission:
Age: Weight: Sex:			Date of Discharge:

Social History:

Family History:

Medical History:

Medication History:

Co-morbidities:

Final Diagnosis:

Year of diagnosis of psychiatric illness: Duration of illness:

Hyponatremia: yes   ☐   no   ☐   Year of diagnosis of hyponatremia:

Frequency of Monitoring for hyponatremia:

Readmission: ☐ Yes   ☐ No

Routine Biochemical Investigations:	
Urea : Tch : T. Bill : S. Cr. : TGs : D. Bill : Na : HDL : T. Prot : K : LDL : Alb : FBS : Glob : PPBS : AST : RBS : ALT : HbA1c :	Others:
Signs and Symptoms of illness:	Severity scores:

	HAM-D Score: PANNS: BADDS: Y-BOCs:

List of drugs administered									
Sl. No	Brand Name	Generic Name	Dose	Frequency	Start Date	End Date	Given at Discharge	No. of Days	Cost

Identification of Risk factors associated with Hyponatremia in Psychiatric patients undergoing treatment: A Case Control Study