DRUGS AND DELIRIUM: A PROSPECTIVE STUDY ON PSYCHOLOGICAL IMPACT

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***Abstract*— Drug induced delirium is reported in intensive care unit patients, especially in the Geriatrics, polypharmacy, pre-disposing drug sensitivities or in improper drug regimens. The most common types of delirium in these cohort patients are hypoactive and mixed-type of delirium which develops in 2-24 hours from admission. As per a study, delirium is known to develop due to an imbalance in the synthesis, release, and inactivation of some neurotransmitters, specifically by acetylcholine deficiency and dopamine activation. Delirium usually presents as a group of symptoms with an acute onset and a fluctuating course which have been categorized into cognitive and behavioral groups. This is a prospective observational cohort study conducted at Gleneagles Aware Global Hospitals, L.B Nagar, Hyderabad for a study period of six months. 200 patients admitted with the hospitalization history of more than 24 hours in critical care units were enrolled as study population. Patient data collection form, contains the socio-demographic details of the patients and Observational study Informed Consent form was prepared for patients understanding for agreeing to participate in the study. The psychological distress assessment was done using CAM-ICU Worksheet and NEECHAM Confusion Scale. In this study, drugs being the major factor to affect the delirium development (at least once during their course of hospitalization) were assessed. It is concluded that Haloperidol and lorazepam administration in the critically patients showed no clinical significance in the development. However other Benzodiazepines administered showed clinical significance (p-value 0.342) with development of delirium, indicating ICU patients are at risk of developing drug induced delirium at a probability of 3.42% as per thus study, which is temporary within the ICU during the course of hospitalization (resolves with relevant patient orientated management) and should be closely monitored during the course of hospitalization.**

***Index Terms*— Benzodiazepines, Critical care, CAM-ICU, Drug-induced, Delirium, Evidence-based study, Haloperidol, ICUS, Intensive care unit, Lorazepam, Observational, Prospective, Terminal care.**

I. INTRODUCTION

The intensive care unit (ICU) syndrome is a range of psychological reactions leading to organic brain dysfunction, including fear, anxiety, depression, hallucinations, fluctuating levels of consciousness and delirium. ICU syndrome could be a temporary disorder in which the patient experiences a cluster of significant psychological symptoms, which can be within the sort of reversible mental illness, delirium or acute brain failure [1]. Delirium is majorly associated with anticholinergic activity that is drugs of different classes, including the tricyclic antidepressants and high-dose anti-epileptics constitute to higher-risk. A majority of drugs such as benzodiazepines, sedatives, Dopaminergic agents, Antiepileptic, Histamine H2 receptor antagonists, Digitalis and Analgesics are reported to be less frequently associated and constitute a moderate risk [2]. A better exploration is required in the aspects of mechanism & factors that affect the sleep deprivation and delirium, which can be implemented in the development of new methods for preventing and control of aggravating outcomes in the critically ill patients [4].

The most widely used scale for assessing delirium in critically ill patients is Confusion Assessment Method for Intensive Care Unit (CAM-ICU) which can be used at beside in nonverbal mechanically ventilated patients. Four main features that are important for assessing delirium in CAM-ICU are:

Acute Onset or Fluctuating Course, Inattention, altered level of Consciousness, Disorganized Thinking. Few studies indicate different sensitivities for the CAM-ICU. This difference in sensitivities can be illustrated by a wide range of heterogeneity seen in the patients included in the study but mainly by a different level of training and experience among the assessors involved in the reviews. Thus, it is difficult to demonstrate with what efficacy these instruments work without adequate preparation, but it is sensible to state that a considerable proportion of critically ill patients with delirium remain undiagnosed if these instruments are applied without proper training to the health care providers. In recent times, two systematic reviews evaluated the accuracy of CAM-ICU [11,12] and concluded that it is an accurate instrument for the diagnosis of delirium in critically ill patients. However, in the only study which was conducted in a non-research setting, most of the delirious patients were not detected by CAM-ICU [11,13].

The NEECHAM (Neelon and Champagne) Confusion Scale contains nine scaled parameters divided into three levels. Each level provides three characteristic parameters. Level-I deals with information processing and orientation (score ranging from 0 – 14 points). It evaluates components of cognitive status: attention and alertness, verbal and motor response, and memory and orientation. Level-II deals with behavior (score ranging from 0 – 10 points). It evaluates behavior and performance ability: general appearance and posture, sensory-motor performance, and verbal responses. Level-III deals with physiological control (score ranging from 0 – 6 points). It evaluates vital function stability: vital signs, oxygen saturation stability and urinary continence control. The total NEECHAM scale score is the product sum of the scores on the three scales. The scale can be rated in 5-10 minutes from observations and measurements of vital signs. The ratings may range from 0-30 where zero indicates minimal function and 30 means normal function; the threshold point is 24. The score from 0–24 points indicates delirium as three types: mild, moderate and severe [14].

Epidemiology:

The medical practitioner ought to take into account delirium, or acute central nervous system pathology, as the brain's type of "organ pathology." Delirium is very common in ICU patients because of factors like comorbidity, critical ill health, and iatrogenesis. This complication of hospital stay is very risky in older persons and has associated with prolonged hospital stays, institutionalization, and death. In summary, an intensive care unit psychopathy doesn't develop in all patients. Instead, several patients are in danger of hypoactive, hyperactive, or mixed hypoactive and hyperactive delirium [3].

Etiology:

- Analgesics: Narcotics such as Meperidine*, Non-steroidal anti-inflammatory drugs*.
- Antibiotics: Fluoroquinolones*.
- Anti-emetics: Scopolamine, Dimenhydrinate.
- Antihistamines such as Chlorpheniramine, Diphenhydramine, Hydroxyzine
- Cardiovascular agents: Antiarrhythmic, Digitalis*, Antihypertensive (beta-blockers, methyldopa)
- Central acting agents: Sedative hypnotics such as benzodiazepines, Anticonvulsants such as barbiturates, Antiparkinsonism agents such as Benztropine, Trihexyphenidyl
- Gastrointestinal agents: Antispasmodics, H2-blockers*.
- Liquid medications containing alcohol.
- Miscellaneous: Skeletal muscle relaxants, Steroids.
- Psychotropic medications: Tricyclic antidepressants, Lithium*.

* Requires dose adjustment in renal dysfunction patients [2].

Pathophysiology:

Drug induced delirium in the ICU patients affects various neurotransmitter pathways in the brain: up-regulation of the postsynaptic glutamate receptor that is NMDA type (mediates the postsynaptic excitatory effects of glutamate), activation of the inhibitory gamma-aminobutyric acid-A (GABA-A) receptor resulting in GABA inhibition and reduced resultant influx of chloride ions, interactions between serotonin and dopamine receptors [8]. Activation of dopamine triggers the delirium occurrence and thus dopamine blockers are used in providing symptomatic relief of delirium (Figure 1).

Anticholinergic Hyperactivity or intoxication triggers a classical delirium syndrome that could be reversed with cholinesterase inhibitors such as physostigmine. Drugs that block muscaranic receptors can also lead to delirium. Some of the drugs such as digoxin, lithium, and histamine (H2)-antagonists manifest to measurable cholinergic receptor binding, even though they are not classified as anticholinergic agents [2]. Digoxin along with its muscarinic antagonistic property, also inhibits membrane $Na^{+}K^{+}ATP^{ase}$, which causes disruption of neuronal activity in the hypothalamus [5]. Quinolone antibiotics which are GABA-A receptor antagonists and NMDA receptor agonists, also possess weak dopaminergic activity, inducing delirium [6, 7].

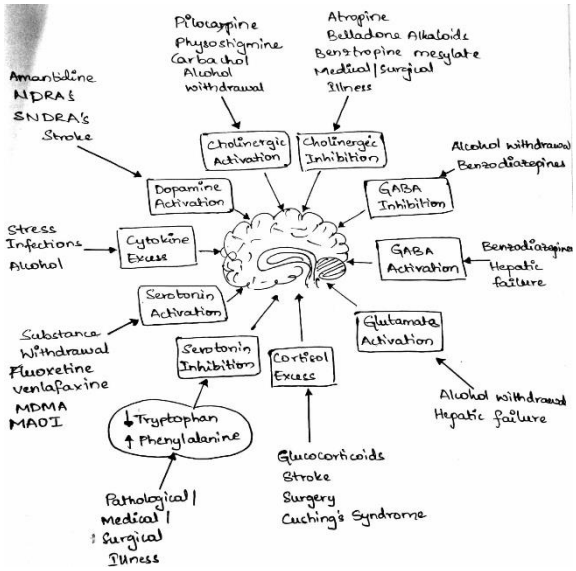

Figure 1: Brief diagrammatic representation of drugs inducing delirium pathophysiology

Clinical manifestations:

Delirium usually presents as a group of symptoms with an acute onset and a fluctuating course. These symptoms have been categorized into cognitive and behavioral groups. Cognitive symptoms include disorientation, inability to assist attention, diminished visuospatial ability, altered level of consciousness and impaired short-time memory. Behavioral symptoms include disturbed sleep-wake cycle, hallucinations, irritability, and delusions [10].

Pharmacotherapy:

In case of drugs induced delirium, few agents are clinically used to manage symptoms of delirium,

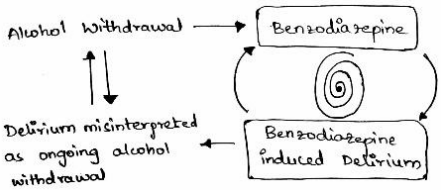

Figure 2: Benzodiazepines inducing delirium hypothesis

especially agitation and aggression. Antipsychotics such as Haloperidol are reported to be the drug of choice for treatment, as it has the least adverse outcomes for short-term duration in delirious patients [9]. Haloperidol possesses low anticholinergic activity and is used for a short period for most of cases with delirium in the ICU settings. Atypical antipsychotics however possess higher anticholinergic activity, and hence have not been explored adequately in the treatment of delirium. Dexmedetomidine, a highly selective alpha-2 adrenergic agent, may be used as an adjunctive for delirious patients in the ICU [15]. In contrast, treatment with haloperidol or chlorpromazine resulted in remarkable improvement in the symptoms of delirium and low incidence of its side effects, whereas treatment with lorazepam had no growth from delirium, instead developed treatment-related adverse effects [16].

Thus, the use of benzodiazepines for the treatment of delirium in critically ill patients is avoided, and in fact, they are believed to be an essential risk factor for developing the delirium (Figure 2). Limiting the use of benzodiazepines in ICU may decrease the incidence of delirium. However, in alcohol withdrawal patients, use of lorazepam is recommended [17].

Non-pharmacological Management:

Non-pharmacological approaches, such as physical and occupational therapy, decrease the duration of hospital and ICU stay and also provide better management of delirium and hence should be encouraged. Review all the drugs in the medication regimen and evaluate if any temporal relationship is present. Monitor the recent addition of a new drug or an increase in dosage of prior drug. Withdraw/taper the dose of drug suspected to induce delirium and re-assess the patient after withdrawal. Avoid

anticholinergic agents, if possible. Reassess pain and add analgesic if required, or reduce the dose or avoid narcotics if high doses have been administered. Avoid all benzodiazepines if possible after dose tapering (1-2 weeks). Closely monitor the creatinine clearance and adjust the dosage of renally eliminated medications in patients with renal dysfunctions. Monitor specific antidotes administrated in poisoning or toxicities. If required, antipsychotics (haloperidol is the drug of choice) could be used to control the behavioural symptoms of delirium. Monitor polypharmacy and use non-delirium causing drugs if possible. If drugs with known risk of inducing delirium are to be used, then close evaluation and monitoring is mandatory for better patient outcomes [2]. To prevent ICU delirium, several critical care units are: Providing periods for sleep, Using more liberal visiting policies, Preventing the patient from unnecessary excitement, Orienting the patient to date, time and place, Asking the patient if there are any concerns, Communicating with the family to obtain information regarding cultural and religious beliefs, Coordinating ICU lights with the normal day-night cycle, Monitoring patient's fluid and nutrition status, Reorientation methods, Avoiding physical restraints correction of sensory deficits, Behavior modification, Usage of ear plugs in prevention of agitation induced by instrumental beeping and sounds, Psychiatric consultation (if required).

II. OBJECTIVE

To assess and evaluate the drugs inducing delirium epidemics in a tertiary care hospital, specifically in the critically ill patients. To evaluate and provide management approaches to overcome this hurdle and to achieve better therapeutic outcomes.

III. METHODOLOGY

This is a prospective observational cohort study conducted at Gleneagles Aware Global Hospitals, L.B Nagar, Hyderabad. for a study period of six months. 200 patients admitted with the hospitalization in the Intensive Critical Care Unit, Medical Intensive Care Unit, Cardiac Intensive Care Unit, Respiratory Intensive Care Unit were enrolled as study population. Subjects with age limit greater than or equal to 18 years with history of hospitalization into critical care for at least 24 hours were included in the study. Pregnant and lactating women, pediatric patients and patients with history of psychological illness & dysfunctions were excluded from the study. Patient data collection form, contains the socio-demographic details of the patients and Observational study Informed Consent form was prepared for patients understanding for agreeing to participate in the study. The drugs suspected for inducing delirium and delirium assessment was done using CAM-ICU Worksheet and NEECHAM Confusion Scale. Patient relevant data for the study was obtained from patient case records, ICU charts, medication charts, directly from patient/ attenders.

IV. RESULTS AND DISCUSSION

Among 200 patients admitted into to the ICU, 05 patients were found to have been administered with haloperidol (2.50%) and 195 patients were not administered haloperidol (97.50%) (Table 1, Figure 3).

Haloperidol	No. of subjects	% of subjects
NO	195	97.50
YES	5	2.50
TOTAL	200	100.00

Table 1: Distribution of patients based on Haloperidol administration

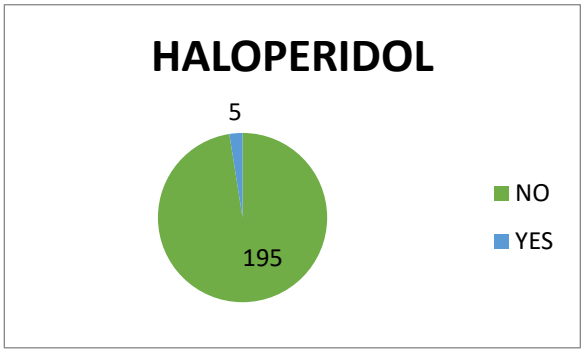

Figure 3: Distribution of patients based on Haloperidol administration

Among 200 patients admitted into to the ICU, 5 patients were administrated with haloperidol out of which 01 developed mild, 03 developed moderate and 01 developed severe type of delirium. Whereas among 195 patients found to be not on haloperidol, 32 developed mild, 32 developed moderate, 54 developed severe delirium and 77 were assessed to be

non-delirious. From the P-value 0.060 the correlation between haloperidol use and delirium development was not clinically significant. Hence there is no significant probability to state that use of Haloperidol tends to enhance the risk of developing delirium in critically ill patients (Table 2, Figure 4).

Haloperidol	Delirious				Total	P-value
	Mild	Moderate	Severe	No		
NO	32	32	54	77	195	
YES	1	3	1	0	5	0.060
TOTAL	33	35	55	77	200	

Table 2: Correlation of ICU delirium with Haloperidol administration

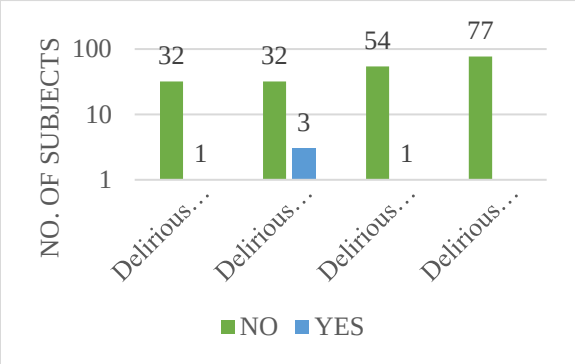

Figure 4: Correlation of ICU delirium with Haloperidol administration

Among 200 patients admitted into to the ICU, 22 patients were found to have been administered Lorazepam (11.00%) and 178 patients were not administered lorazepam (89.00%) (Table 3, Figure 5).

Lorazepam	No. of subjects	% of subjects
NO	178	89.00
YES	22	11.00
TOTAL	200	100.00

Table 3: Distribution of patients based on Lorazepam administration

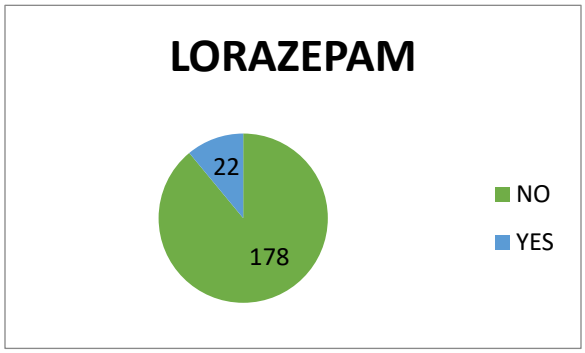

Figure 5: Distribution of patients based on Lorazepam administration

Among 200 patients admitted into to the ICU, 22 patients were administrated with lorazepam, out of which 04 developed mild, 05 developed moderate, 05 developed severe type of delirium and 08 were non delirious. Whereas among 178 patients found to be not on lorazepam, 29 developed mild, 30 developed moderate, 50 developed severe delirium and 69 were assessed to be non-delirious. From the P-value 0.882 the correlation between benzodiazepine use (other than lorazepam) and delirium development was not clinically significant. Hence there is no significant probability to state that use of lorazepam tends to enhance the risk of developing delirium in critically ill patients (Table 4, Figure 6).

Lorazepam	Delirious				Total	P-value
	Mild	Moderate	Severe	No		
NO	29	30	50	69	178	
YES	4	5	5	8	22	0.882
TOTAL	33	35	55	77	200	

Table 4: Correlation of ICU delirium with lorazepam administration

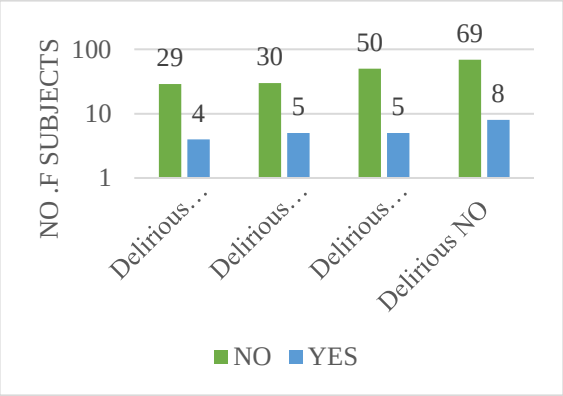

Figure 6: Correlation of ICU delirium with lorazepam administration

Among 200 patients admitted into to the ICU, 27 patients were found to have been administered Benzodiazepines other than Lorazepam (13.50%) and 173 patients were not administered Benzodiazepines (86.50%) (Table 5, Figure 7).

Benzodiazepines	No. of subjects	% of subjects
NO	173	86.50
YES	27	13.50
TOTAL	200	100.00

Table 5: Distribution of patients based on Benzodiazepines administration (other than Lorazepam)

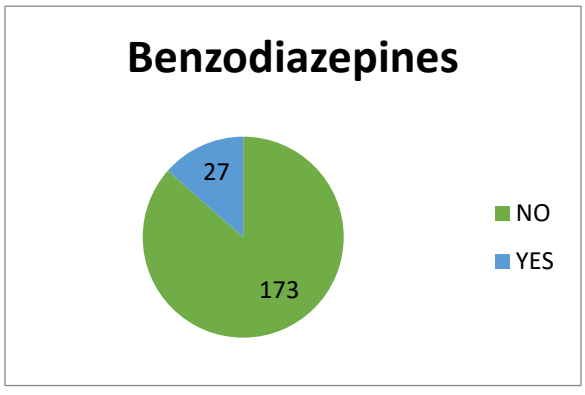

Figure 7: Distribution of patients based on Benzodiazepines administration (other than Lorazepam)

Among 200 patients admitted into to the ICU, 27 patients were administrated with benzodiazepines (other than lorazepam), out of which 04 developed mild, 08 developed moderate, 07 developed severe type of delirium and 08 were non delirious. Whereas among 173 patients found to be not on any benzodiazepines, 29 developed mild, 27 developed moderate, 48 developed severe delirium and 69 were assessed to be non-delirious. From the P-value 0.342 the correlation between benzodiazepine use (other than lorazepam) and delirium development was clinically significant. Hence the use of benzodiazepines tends to enhance the risk of developing delirium in critically ill patients (Table 6, Figure 8).

Benzodiazepine	Delirious				Total	P-value
	Mild	Moderate	Severe	No		
NO	29	27	48	69	173	
YES	4	8	7	8	27	0.342
TOTAL	33	35	55	77	200	

Table 6: Correlation of ICU delirium with Benzodiazepines administration other than lorazepam

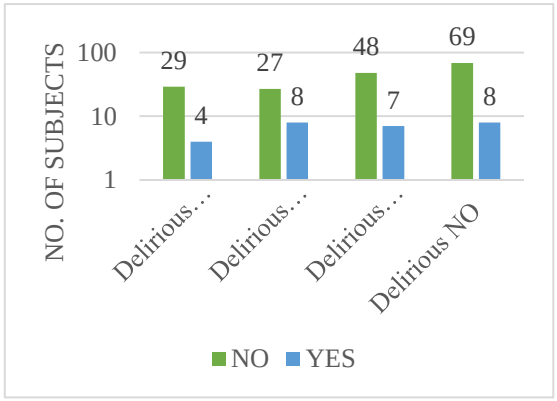

Figure 8: Correlation of ICU delirium with Benzodiazepines administration other than lorazepam

V. CONCLUSION

In this study, drugs being one of the major factors to affect the delirium development (at least once during their course of hospitalization) are clinically evaluated using the probability value. It is concluded that Haloperidol and lorazepam administration in the critically patients showed no clinical significance in the development (Table 2,4 and Figure 4,6). However, other Benzodiazepines administered showed clinical significance (p value 0.342) with development of delirium (Table 6, Figure 8), indicating ICU patients are at risk of developing drug induced delirium at a probability of 3.42% as per thus study, which is temporary within the ICU during the course of hospitalization (resolves with relevant patient orientated management) and should be closely monitored during the course of hospitalization.

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