JSS ACADEMY OF HIGHER EDUCATION & RESEARCH
(DEEMED TO BE UNIVERSITY) MYSURU

CLINICAL PHARMACY NEWSLETTER

A Newsletter of Drug and Prescribing Information

Published by
Clinical Pharmacy Services Department, Govt. Medical College & Hospital, Ooty
(A Unit of Department of Pharmacy Practice, JSS College of Pharmacy, Ooty)

Volume XXVIII Issue 03

JULY - SEPTEMBER 2022

INSIDE THIS ISSUE

Sequential and Combination HBV Treatment with Polymerase Inhibitors- An overview

HBV continues to be a major source of illness and mortality worldwide, despite the introduction of an effective vaccination in 1986. HBV is a significant cause of cirrhosis and hepatocellular cancer and infects many millions of people every year. The hepatitis B virus (HBV) is a tiny DNA-encapsulated virus that infects primates, rodents, and birds. It is the main cause of chronic hepatitis B. These viruses all have a high degree of species and cell type selectivity, as well as an odd genomic and replication organization resembling that of retroviruses. The HBV virion is made up of an exterior lipid envelope and an internal icosahedral protein capsid that houses the viral genome and a DNA polymerase that also acts as reverse transcriptase. Multiple intracellular viral proteins, such as HBx, HBcAg, and HBV polymerase, are critical for HBV replication.

The first method designed to treat CHB was the use of interferon (IFN), an immune modulator. Since Peg-pegylated IFN's version (Peg-IFN) has a substantially longer half-life and a more persistent virologic response, it has supplanted IFN, which was licensed in 1991. The powerful polymerase inhibitors known as nucleos(t)ide analogs (NAs), sometimes referred to as NRTIs, act as chain terminators by incorporating into replicated DNA and specifically target the viral polymerase elongation process. Initially, lamivudine, also known as 3TC, was used, but because of the prevalence of HBV polymerase gene mutations or variations capable of evading its action, additional NRTIs, including entecavir (ETV) and tenofovir, was also used. Current immunomodulators do not target a specific HBV function but augment the body's natural immune defense. As such, they are not associated with specific HBV mutations. The HBV polymerase enzyme, a reverse transcriptase, is the target of all currently available oral antivirals. This enzyme carries out a variety of tasks necessary for the HBV replication cycle, including viral RNA binding, RNA packaging, protein priming, template switching, DNA synthesis, and RNA destruction. In addition, HBV polymerase requires host proteins to function. The HBV polymerase contains several important domains and motifs that define its functions and provide additional ways to target it. Four domains make up the HBV polymerase. They are the spacer domain, the RT domain, which contains the polymerase activity, the RNase H domain at the carboxy-terminus, which is crucial for eliminating template RNA, and a terminal protein (TP) at the amino end that is significant for early DNA synthesis. The TP, RT, and RNase H domains are crucial for polymerase operation, and each might serve as a therapeutic target.

More treatment strategies that target various stages of the HBV lifecycle have lately been tested. HBV polymerase is one of the most effective treatment targets and polymerase inhibitors strongly block rcDNA formation and, thereby, inhibit intracellular cccDNA amplification. The development of new polymerase inhibitors remains a major challenge, even though cccDNA-targeted medications appear to have a lot of promise. However, the difficulty of eliminating covalently closed circular (ccc) DNA is a crucial problem that must be tackled in hepatitis B virus (HBV) infection. Currently, most of the treatment for those with chronic hepatitis B virus (HBV) infection is oral nucleoside/ nucleotide analogues (NAs). In general, using them is safe. The nucleoside and nucleotide analogs currently used against HBV in the clinic are clevu-dine, emtricitabine, entecavir, lamivudine and telbivudine (nucleosides); and adefovir dipivoxil and tenofovir disoproxil fumarate (nucleotides). But the long-term NRTI monotherapy may promote the establishment of viral strains that are resistant to the treatment. As a result of its cumulative and even synergistic inhibitory effects against even drug-resistant mutants, combination therapy to inactivate viruses from many aspects is an appealing technique for treating viral infections. It has been demonstrated that sequential "switching to combination," which involves beginning with one therapy and moving on to another, is more successful than simultaneous-combination therapy. According to several studies, the sequential administration of a one or two-year course of NRTI (predominantly ETV) followed by interferon for 48 or 60 weeks raised the loss rate of HBsAg in CHB patients from 32 to 36%. However, only 0 or 4.3% of patients saw HBsAg loss while receiving an NRTI by itself.

The two NRTIs suggested as first-line treatment (in addition to interferon) have very low cumulative resistance rates. Adefovir, emtricitabine, lamivudine, and telbivudine all have higher 5-year resistance rates, ranging between 30 and 70%. Telbivudine is like lamivudine, but more potent and associated with less resistance. According to several studies, peg-IFN combined with ETV or TDF in a simultaneous, sequential, or add-on combination treatment produces more

favorable therapeutic outcomes. It is crucial to create therapeutic medications that target several life cycles in addition to the polymerase itself, such as NNRTIs, if HBV infection is to be treated with combination therapy. The direct binding of NNRTIs to the polymerase results in a conformational shift that interferes with the active site's ability to perform polymerization, which then results in the loss of activity.

There are currently numerous agents that have at least shown this as proof of principle, making the attempt to cause HBsAg loss a better alternative. NAP- Nucleic Acid Polymers, TDF- Tenofovir Disoproxil Fumarate, and PEG-IFN together provide the highest HBsAg loss rates, however, PEG-IFN dependence makes this combination difficult to tolerate. Although they are currently in early-stage research, TLR8 and PD-1 medicines have the potential for HBsAg loss. It is yet unknown whether PD-1 agonists are safe, and the therapeutic dosage and duration have not yet been optimised. Combination therapy is certainly required and the combination of reducing HBsAg load and immune stimulation seems strategic but remains to be proven. Alternatively, combining agents that strongly affect HBsAg production such as NAP and siRNA- small interfering RNA or ASO- Antisense Oligonucleotide should also be explored. There are likely to be multiple pathways to achieve functional cure, but the optimal strategy is still unclear. Consequently, the outcome of HDV cure and HBsAg loss are tied together.

References:

1. Mak LY, Seto WK, Lai CL, Yuen MF. DNA polymerase inhibitors for treating hepatitis B: a safety evaluation. Expert Opin Drug Saf. 2016;15(3):383-92. doi: 10.1517/14740338.2016.1139573. Epub 2016 Feb 1. PMID: 26752687.

2. Ohsaki E, Suwanmanee Y, Ueda K. Chronic Hepatitis B Treatment Strategies Using Polymerase Inhibitor-Based Combination Therapy. Viruses. 2021 Aug 26;13(9):1691. doi: 10.3390/v13091691. PMID: 34578273; PMCID: PMC8473100.

3. Clark DN, Hu J. Unveiling the roles of HBV polymerase for new antiviral strategies. Future Virol. 2015;10(3):283-295. doi: 10.2217/fvl.14.113. PMID: 25893003; PMCID: PMC4399241.

4. Tan, YC, Lee, GH, Huang, DQ, Lim, SG. Future anti-HDV treatment strategies, including those aimed at HBV functional cure. Liver Int. 2022; 00: 1- 13. doi:10.1111/liv.15387

5. Loglio A, Viganò M, Lampertico P. Novel Therapies That May Cure Chronic Hepatitis B Virus. Clin Liver Dis. 2021 Nov;25(4):875-899. doi: 10.1016/j.cld.2021.07.001. PMID: 34593159.

Carbapenem resistant bacteria emerging in community settings-An Alarming finding

A new study from the Centers for Disease Control and Prevention (CDC) found that a surprising proportion of cases of carbapenem-resistant Enterobacterales (CRE) are found in isolates from patients in the community (CA-CRE). They had previously been thought to be healthcare-associated infections (HCA-CRE). Traditionally, CRE has been thought of as a nosocomial infection, acquired in a hospital or other healthcare facility (nursing home, long-term acute care hospital, dialysis center, etc.). This is the first population-level study to show otherwise, with fully 10% of the CRE isolates found to be community-acquired.

CREs are a group of multidrug-resistant bacteria considered an urgent health threat by the CDC because they can rapidly spread between patients, especially those who are most seriously ill and vulnerable, and because they are so difficult to treat. These patients often require treatment with toxic antibiotics, such as colistin, and carry a high mortality rate — up to 50% in some studies.

Overall, 30% of CREs carry a carbapenemase — an enzyme that can make them resistant to carbapenem antibiotics. The genes for this are readily transferable between bacteria and help account for their spread in hospitals.

In a recent study, published in the American Journal of Infection Control, of the 12 isolates that underwent whole-genome sequencing, 42% of the CA-CRE isolates carried the carbapenemase gene. The findings highlight the potential for CP-CRE to move from healthcare settings into the community. The fact that 5 of the 12 isolates harbored a carbapenemase gene introduces new challenges for controlling spread of CP-CRE.

CDC researchers analyzed data from eight US metropolitan areas between 2012 and 2015 as part of CDC's Emerging Infections. Program (EIP) healthcare-associated infections — community interface activity, which conducts surveillance for CRE and other drug-resistant gram-negative bacteria. Cases of CA-CRE were compared with HCA-CRE, with 1499 cases in 1194 case-patients being analyzed. Though Klebsiella pneumoniae was the most common isolate, there were some differences between metropolitan areas. The incidence of CRE cases per 100,000 population was 2.96 (95% CI, 2.81-3.11) overall and 0.29 (95% CI, 0.25-0.25) for CA-CRE. Most CA-CRE cases were in White persons (73%) and women (84%). Urine cultures were the source of 98% of all CA-CRE cases, compared with 86% of HCA-CRE cases (P < .001)

Though small numbers, the numbers of patients with CA-CRE without apparent underlying medical condition (n = 51, 37%) was greater when compared with patients with HCA-CRE (n = 36; 3%; P < .001).

The study stated that 10% of patients with CA-CRE acquired it in the community. This is an increasingly serious problem for women, because with a community-acquired bladder infection, patients usually tend to go to physicians or an emergency care, where physicians are forced to prescribe an empirical antibiotic. The study also concluded that, because of such empiric treatment and increasing resistance, the risk for treatment failure is quite high, especially for older women.

References:

- Bulens SN, Reses HE, Ansari UA, Grass JE, Carmon C, Albrecht V, Lawsin A, McAllister G, Daniels J, Lee YK, Yi S. Carbapenem-Resistant enterobacterales in individuals with and without health care risk factors—Emerging infections program, United States, 2012-2015. American Journal of Infection Control. 2022; 1-8.

DRUG PROFILE

PRALSETINIB

Pralsetinib is used to treat a certain type of non-small-cell lung cancer (NSCLC) in adults that has spread to other parts of the body. It is also used to treat a certain type of thyroid cancer in adults and children 12 years of age and older that is getting worse or that has spread to other parts of the body. Innovator-Blueprint Medicines Corporation. Massachusetts, United States. The drug was first FDA approved on September 4, 2020.

Indication:

Pralsetinib is used to treat a certain type of non small-cell lung cancer (NSCLC) in adults that has spread to other parts of the body.

Approved Indication:

- Non-Small Cell Lung Cancer
- Medullary Thyroid Cancer
- Thyroid Cancer

Mechanism of Action:

Pralsetinib is a tyrosine kinase inhibitor of wild-type RET and oncogenic RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M and RET M918T). It exhibited anti-tumor activity in cultured cells and animal tumor implantation models harboring oncogenic RET fusions or mutations including KIF5B-RET, CCDC6-RET, RET M918T, RET C634W, RET V804E, RET V804L and RET V804M.

Certain RET fusion proteins and activating point mutations can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to uncontrolled cell proliferation. Pralsetinib exhibited anti-tumor activity in cultured cells and animal tumor implantation models harboring oncogenic RET fusions or mutations including KIF5B-RET, CCDC6-RET, RET M918T, RET C634W, RET V804E, RET V804L and RET V804M. In addition, pralsetinib prolonged survival in mice implanted intracranially with tumor models expressing KIF5B-RET or CCDC6-RET.

Dosage Form and Administration:

The recommended dosage of Pralsetinib is 400 mg orally once daily on an empty stomach (no Food intake for at least 2 hours before and at least 1 hour after taking Pralsetinib). Continue treatment until disease progression or until unacceptable toxicity.

Dosing in renal and hepatic impairment:

No dosage adjustment necessary for Mild-to-moderate (CrCl 30-89 mL/min) renal impairment patients and Severe (CrCl <15 mL/min)- Not studied.

Storage:

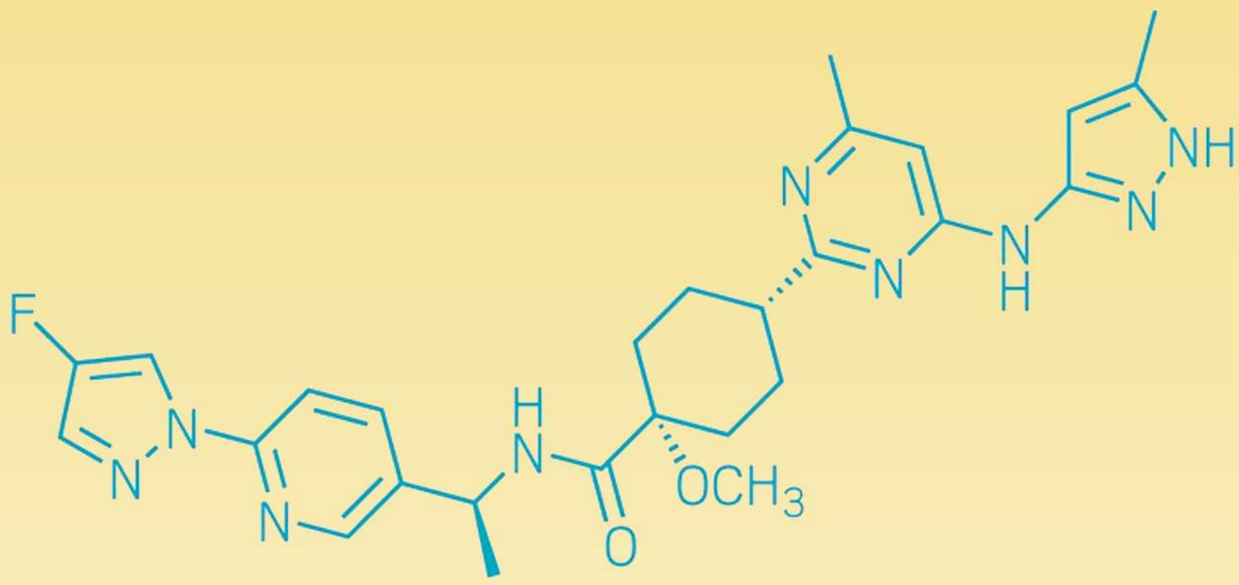
Store at 20°C to 25°C (68°F to 77°F)

Generic Equivalents:

Selpercatinib, Nivolumab

Cost:

INR 250000/- for 60 100 mg Capsules in a box



Pharmacokinetics:

Absorption:

- Tmax, oral: 2 to 4 hours
- Effects of food: Cmax increased by 104%; AUC (0 to infinity) increased by 122%; Tmax delayed by 4.5 hours.

Distribution:

- Protein binding: 97.1%, Vd: 228 L
- Metabolism, Hepatic: Primarily by CYP3A4; to a lesser extent by CYP2D6 and CYP1A2, Oxidation and glucuronide conjugates: Unknown activity, Inducer of CYP2C8, CYP2C9, CYP3A4, and CYP3A5, Inhibitor of CYP3A4, CYP3A5, CYP2C8 and CYP2C9, Inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, MATE2-K, and BSEP transporters, Substrate of CYP3A4, CYP2D6, and CYP1A2, Substrate of P-gp and BCRP

Excretion:

- Renal excretion: 6%; 4.8% was unchanged, Fecal excretion: 73%; 66% was unchanged, Total body clearance: 9.1 L/hr, Elimination Half Life: 22.2 hours

Adverse effects:

- Cardiovascular: Edema (20% to 29%), Gastrointestinal: Constipation (35% to 41%), Diarrhea (24% to 34%), Hepatic: ALT/SGPT level raised (46%), Aspartate aminotransferase serum level raised (69%), Musculoskeletal: Musculoskeletal pain (32% to 42%), Respiratory: Cough (23% to 27%), Pneumonia (17%), Other: Fatigue (35% to 38%)

  Serious Reactions:

  Cardiovascular: Hypertension (28% to 40%), Dermatologic: Impaired wound healing, Hematologic: Hemorrhage, Grade 3 or Greater (2.5%) Hepatic: Hepatotoxicity (2.1%), Immunologic: Sepsis, Respiratory: Pneumonitis (10%)

Contraindications:

Pralsetinib use may increase the risk of hypertension, hemorrhagic events, impaired wound healing, hepatotoxicity, interstitial lung disease/pneumonitis, and embryo-fetal toxicity.

Precautions:

Interstitial Lung Disease (ILD)/Pneumonitis: Withhold GAVRETO for Grade 1 or 2 reactions until resolution, and then resume at a reduced

dose. Permanently discontinue for recurrent ILD/pneumonitis. Permanently discontinue for Grade 3 or 4 reactions.

Hypertension: Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating GAVRETO. Monitor BP after 1 week, at least monthly thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue GAVRETO based on severity.

Drug Interactions:

Strong CYP3A inhibitors: Avoid coadministration.

Combined P-gp and Strong CYP3A inhibitors: Avoid coadministration. If coadministration cannot be avoided, reduce the dose of GAVRETO.

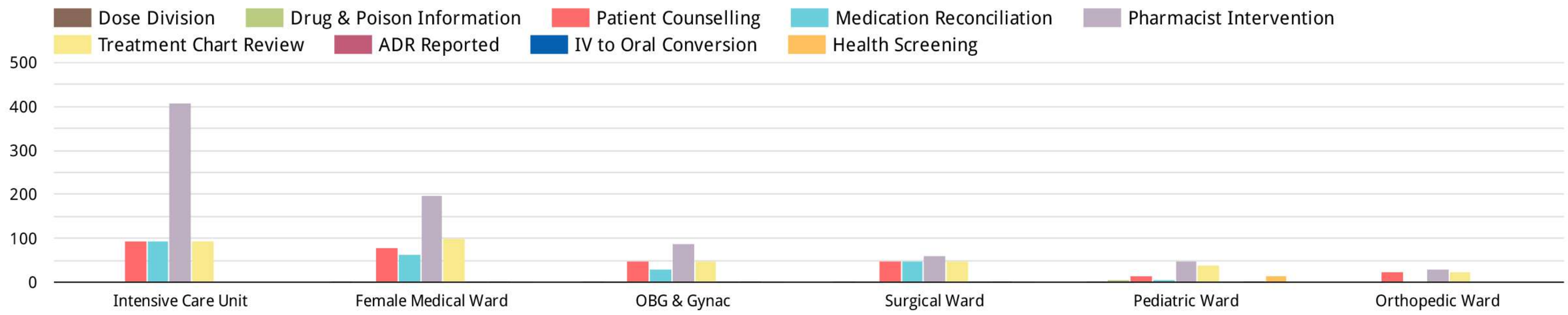
Strong CYP3A inducers: Avoid coadministration. If coadministration cannot be avoided, increase the dose of GAVRETO.

CLINICAL PHARMACY SERVICES REPORTS 2022-2023

1 Jan 2022 - 31 Jul 2022

DEPARTMENT OF PHARMACY PRACTICE
JSS COLLEGE OF PHARMACY , OOTY

JSS ACADEMY OF HIGHER EDUCATION & RESEARCH
(DEEMED TO BE UNIVERSITY) MYSURU



	Ward Name	Pharmacist In...	Medication Re...	Treatme...	Patient Couns...	ADR Reported	Drug & Poison...	Dose Division	IV to Ora...	Health Scr...
1.	Pediatric Ward	49	6	40	16	1	6	0	0	16
2.	Female Medical W...	199	65	101	80	0	0	0	0	0
3.	OBG & Gynac	89	32	48	48	0	0	0	0	0
4.	Surgical Ward	61	48	48	48	0	0	0	0	0
5.	Intensive Care Unit	408	96	96	96	null	null	null	null	null
6.	Orthopedic Ward	31	null	24	24	null	null	null	null	null
	Grand total	**837**	**247**	**357**	**312**	**1**	**6**	**0**	**0**	**16**

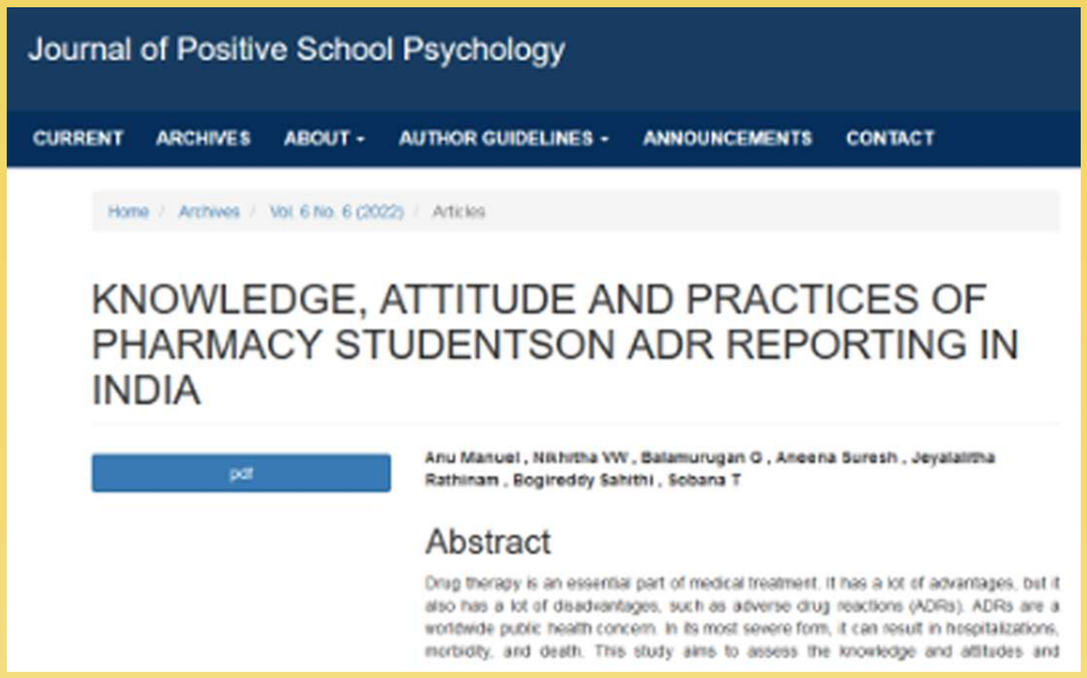
Publications

1. Manuel A, Nikhitha VW, Balamurugan G, Aneena Suresh, Jayalalitha R, Sahithi B, Sobana T. Knowledge, attitude and practices of pharmacy students on ADR reporting in India. Journal of Positive School Psychology. 2022; 6:5994-6005.

2. Philip SM, Aneena Suresh, Priyadharshini G, Ponnusankar S, AP R, Vishwas HN. Assessment of menstrual attitudes and predictors for premenstrual syndrome in University Students Of Ooty, South India. Journal of Positive School Psychology. 2022; 6(6):3736-46.

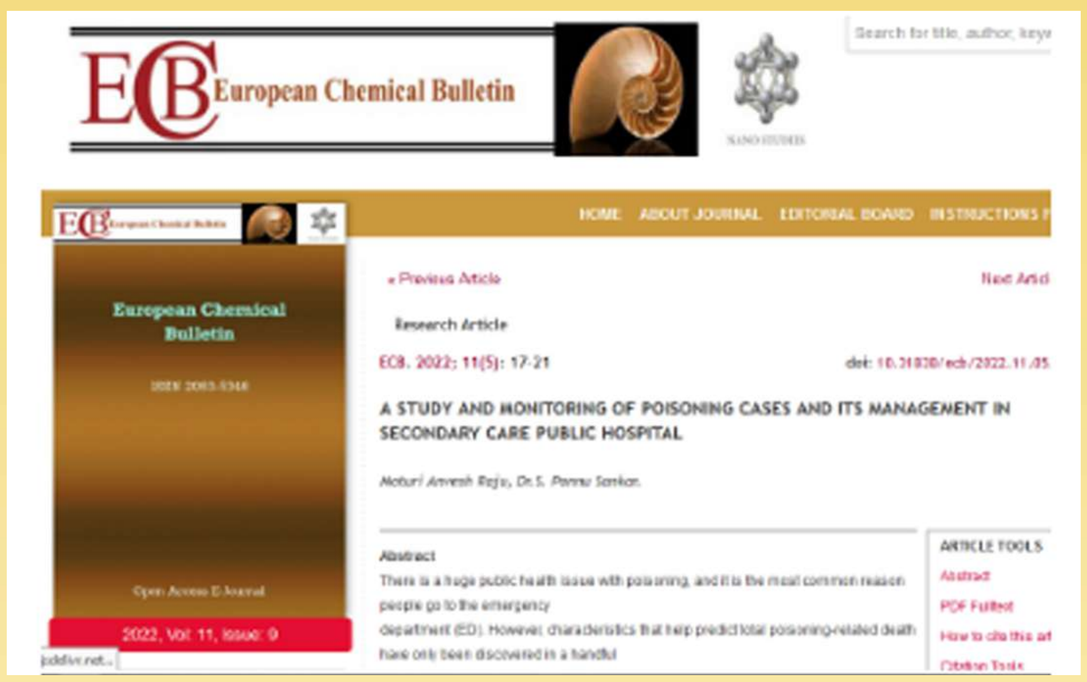
3. Moturi Anvesh Raju, Ponnusankar S. A study and monitoring of poisoning cases and its management in secondary care public hospital. European Chemical Bulletin. 2022; 11(5):17-21.

4. Deepalakshmi M, Inthuja S, Priyanka A, Sanjay M, Shahban Ahamed A, Rinu M. Xavier, Arun KP. The role of pictograms in adverse drug reactions reporting in human immunodeficiency virus positive patients. Chinese Journal of Medical Genetics. 2022; 31(3):447-53

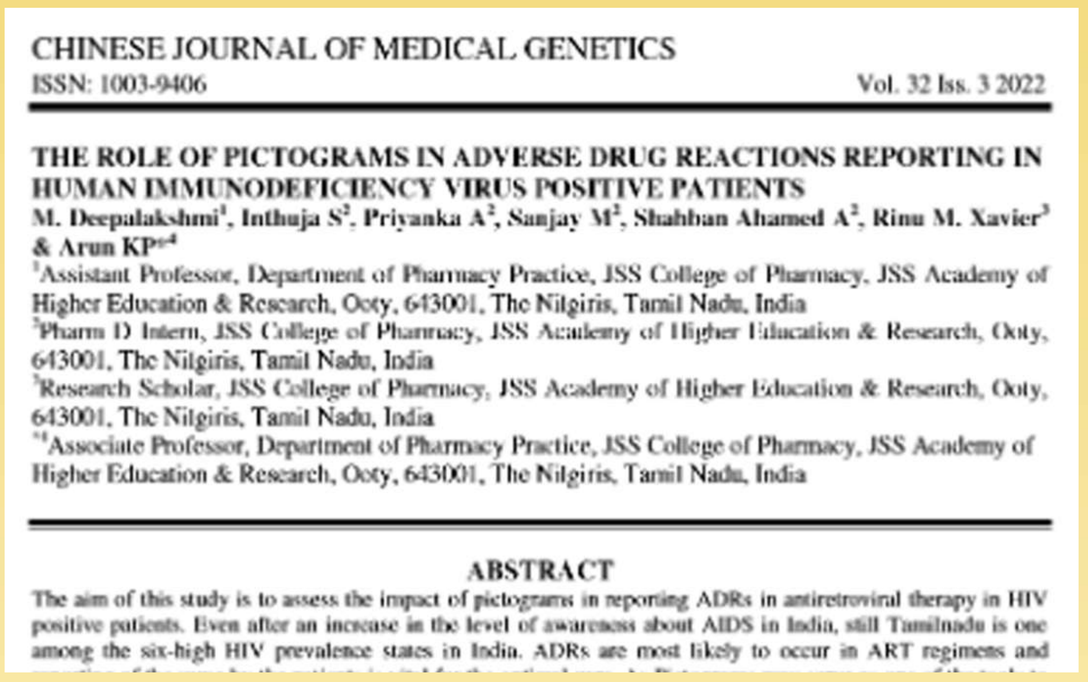


Aneena et all.,2022

Vishwas H N et all.,2022



Ponnusankar et all.,2022



Deepalakshmi et all.,2022

OUTREACH PROGRAM:

OUTREACH Program Report on National Nutrition Week
1st – 7th September 2022

National Nutrition Week Program was organized and celebrated from 1 – 7th September 2022.

Nutrition is the focal point of health and well-being, and it allows you to be strong, provides the individual with the energy to do the things it wants to do, and makes look and feel the best. The aim of the program is to create nutrition awareness through training education, seminars, competitions, road show and campaigns.

National Nutrition Week 2022 program was organized by Dept. of Pharmacy Practice, JSS College of Pharmacy, Ooty between 1 – 7th September 2022.

The programme contents of the nutrition week include:

- Nutrition Awareness - Key to Healthy Nation –Power Point presentations
- Nutrition Awareness Campaign in Community (including Schools)
- Activities and games for middle school children
- Preparation of Nutritious Food charts (to be placed in schools)

Awareness program was organized at Govt. Panchayat Union Middle Schol, KIlkawhatty Village, Ooty; Govt. Panchayat Union Middle School, Odaikadu Village, Ooty and Govt. Panchayath Union Middle School, Glenmorgan Camp, Ooty. The said program was well received by the students of the school and around 225 students benefitted from the program.

Dr C Keerthana and Dr Jeyaram Bharathi, Clinical Resident of our department coordinated this event on behalf of the Dept.

OUTREACH Program Report on World Mental Health Day 2022
6th – 10th September 2022

Department of Pharmacy Practice in association with Indian Pharmaceutical association (Nilgiris Local branch) organized the World Mental Health Day 2022 program for the benefit of our students. The theme of this year celebrations is: Make mental health and well-being for all a global priority.

The program was initiated from 6th of October, remembering the various mental health activities for staff and students. A brain break activity for 5 min was given between classes from 6-10th October that improves concentration of students and calms their mind. Other fun activities included a feelings wheel depicting the various emotions of the staff and students, a wall of gratitude with notes showing what they are grateful for, non-dominant hand challenge where one has to use their weak hand to do all activities which helps to develop new connections to the brain.

On 10th October, the celebrations were started with giving smiley badges and green ribbon to staff and students and explaining the significance of maintaining good mental health. Following this, student games were conducted from 10-11 am, which showcased the active participation from students of all courses.

A webinar on 'Lead a joyful and stress-free life' was presented by Dr. Shilpa Shah, Founder of Swastii Lifestyle medicine and naturopathy clinic, Coimbatore gave insights on causes of poor mental health such as depression and how to overcome them by practicing the right relaxation techniques and breathing exercises. Another interesting online session on 'Management of common mental disorders- pharmacological challenges – an NHS psychiatrist perspective' was made by Dr. Muthukumar Gnanavel, Consultant Psychiatrist, Swansea Bay University Health Board, UK. He explained about the newer techniques in experimental pharmacology and its future applications. Students of 5th & 6th year Pharm D were engaged with a talk on 'It's OK to not be OK' by Dr. Ramesh, Psychiatrist, Govt. Medical College & Hospital, Ooty.

He explained about depression, drug abuse, suicides among students, when a psychiatrist consultation is required and how to overcome negative thoughts in life. Dr Aneena Suresh, Asst. Professor and Dr Mohsina Hyder, Lecturer, Dept. of Pharmacy Practice coordinated event on behalf of the Dept. There was a question-and-answer session where staff and students clarified their doubts related to pharmacovigilance. A total of 96 participants were present in the session.

September17, 2022

July1, 2022

For clarifications/ feedback, write to:

The Chief Editor
Clinical Pharmacy Newsletter,
Department of Pharmacy Practice

Prepared & Circulated by:

Department of Pharmacy Practice
JSS College of Pharmacy,
Rocklands, Udhagamandalam- 643001
The Nilgiris Tamilnadu, India
E-mail ID: pharmacypracticeooty@gmail.com
/drsponnusankar@jssuni.edu.in
Phone: (+91)-423-2443393
Fax: (+91)-423-2442937