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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 16th issue of ESSENCE.

The use of animals for scientific experimental purposes has contributed a great deal to the advancement of biomedical knowledge. The current issue explores the use of ZEBRA FISH in research ranging from Epilepsy, Cognition, Obesity, DM and Neuro-muscular disorders.

Physicians during the course of their work need drug related information all the time. A Drug Information Centre (DIC) can help immensely since they offer unbiased and up-to-date information. A DIC has been established in AIIMS Mangalagiri and would be dedicated towards providing objective, independent and current information on drugs. The role of DIC in health care setup has been highlighted in the current issue.

Drug abuse and their deleterious consequences have led to an increased incidence of criminal and civil litigations. The skills and expertise of an expert with knowledge about drugs and chemicals can be useful in solving a diverse number of legal cases. The current issue has an interesting Guest column on Drug abuse and the role of emerging fields of Forensic Pharmacology and Forensic Pharmacovigilance.

Further, as always, we have recent updates from the world of medicines, new drug approvals, Drug safety alerts, and cross word puzzle quiz on 'Drugs causing Hyponatremia'.

Link to access quiz as under: Winners will be declared in the next issue
https://docs.google.com/forms/d/e/1FAIpQLSfVPlAHeeRnP8beLPuB5pAdMWD9zWIq9OP9RDfid7F3CQKleg/viewform?vc=0&c=0&w=1&flr=0

Happy Reading and Stay Safe.

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Zebrafish (*Danio rerio*) are freshwater fishes founds in Indian water habitats and many other regions. The zebrafish name originates from typical strips located all over the body. Zebrafish is being used in research from as early as 1960s. Zebrafish body consists of brain, mouth, spinal cord, eyes, mouth, esophagus, intestine, bile ducts, kidney, heart, blood, cartilage, bone and teeth and many organs similar to humans. 70% of zebrafish genes are similar to humans. Zebrafish was used as model for genetics of different diseases as early as 1980s in ethyl nitrosourea mutagenesis experiments. Being a small fish and easy to maintain, zebrafish carried several advantages over the traditional rodent models of different diseases. Optical clarity of zebrafish allows live imaging of the developing embryo, easy of generation of tissue specific transgenic zebrafish, ease of Tol2 based controlled gene expression and CRISPER based gene editing tools. Tracking of cellular events at real time basis using live imaging of zebrafish embryo allows us to understand the molecular dynamics of development of different organs and congenital deformities.

Zebrafish as a model of epilepsy:

Zebrafish shows typical features similar to human epilepsy. Zebrafish exposed to pentylene tetrazole (PTZ, 6-10mM conc. in tank water) show epileptiform discharges and is already well characterized clinically (1) and electrophysiologically (2). The zebrafish model of epilepsy also shows features of post epilepsy cognitive dysfunction similar to humans (3). There are many epilepsies severity scores, based upon which, the severity of epilepsy can be quantified for research study perspective:

1. As per Gupta P et al, 2014, the behavioral abnormalities will be characterized as per Stage I (characterized by increase swim activity), Stage II (characterized by the rapid whirlpool-like circling swim behaviors) and Stage III (characterized by a series of brief clonus-like seizures leading to loss of posture, for example fish falls on one side and remains immobile for 1-3 s). Latency to different stages (stage I, II and III) can be compared for identification of potential antiepileptic agents (4).
2. As per Mussulini et al, 2013 (1), the epileptic behavior can be scored as: 0=Short swim mainly in the bottom of the tank, 1=Increased swimming activity and high frequency of opercular movement, 2=Burst swimming, left and right movements, and erratic movements, 3=Circular movements, 4=Clonic seizure-like behavior (abnormal whole-body rhythmic muscular contraction), 5=Fall to the bottom of the tank, tonic seizure-like behavior (sinking to the bottom of the tank, loss of body posture, and principally by rigid extension of the body).

Zebrafish model of cognitive impairment:

Similar to animal models of cognitive impairment (e.g., morris water maze, elevated plus maze), cognitive impairment can be evaluated in zebrafish using different forms of maize. T maze is a well validated model of discriminative learning in zebrafish. Environmental modifications or application of selective stimuli can further enhance the learning process. Another advantage is by slight change of the environment/stimuli, and by giving suitable reward we can further characterize spatial learning and reversal. The maze can also be used to evaluate social preference and social novelty, these parameters play a significant role in in case of evaluation of neurodevelopmental disorders (e.g., autism spectrum disorder). The maze can be further modified using different inserts for specific purposes. Many software's assists behavioural tracking in

zebrafish e.g., ethovision XT. These tools and easy of genetic manipulation making zebrafish models as a suitable model for behavioral experiments.

Neuromuscular development:
dmd$^{ta222a/ta222a}$ strain of zebrafish serves as a model for muscular dystrophy, WT + CRISPR1-*mecp2* [ZDB-FISH-151014-40] serves as a model for rett syndrome etc. Apart from different other models are available to evaluate evaluate specific diseases and to evaluate and gather preliminary data regarding the safety and efficacy of newer agents under evaluation.

Zebrafish as a model for obesity and diabetes:
Owing to the functional similarity of the metabolism of lipid and glucose, adipose tissue biology and structure of pancreatic, zebrafish models serve as a good surrogate for human disease in the field of metabolic disease. Zebrafish body contains many adipose tissue deposition sites and their development is already well characterized. Lipids are stored in subcutaneous, intramuscular and visceral lipid stores in zebrafish, which is quite similar to humans. BMI, and quantification using CT scan are important measures to quantify human adiposity, however, doing the same is quite difficult in zebrafish. In this regard different techniques are being used to visualize lipids in zebrafish e.g., using different dyes in histologic sections (sudan black B, oil red o, nile red etc.). In addition, variety of fluorescent lipid analogues and tracers are available, which can help us in quantifying the same. High fat diet model is an important model of zebrafish obesity. Genetic model of obesity in zebrafish is also established by overexpressing AgRP (Agouti related peptide).
Coming to the structure of pancreas in zebrafish, it contains both endocrine and exocrine components, and the components of the endocrine compartment being alpha cells (produce glucagon), beta cells (produce insulin), δ cells (produce Somatostatin), ε-cells (produce ghrelin) and PP cells arranged in a similar manner to mammals. Regarding zebrafish model of experimental diabetes, some of the important models are induced by pancreatectomy, chemical ablation (complete and partial ablation using streptozotocin, mimicking type 1 and type 2 diabetes respectively), and over-nutrition models. These models played important role in evaluation of safety and efficacy of newer chemical entities and understanding the pathophysiological and mechanistic basis of diabetes.

Conclusion: Owing to high genetic homology to human genome and highly conserved physiologic processes between zebrafish and mammals, zebrafish models are currently gaining lots of importance. However, translatability varies from disease to disease depending upon the extent of validity of different models.

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Recent new/Update from the world of medicines ….

Early Metformin Minimizes Anti-Psychotic Induced Weight Gain

Psychiatrists should consider prescribing Metformin early to patients who experience rapid weight gain after initiation of Anti-Psychotic drugs, according to a new evidence-based guideline. The investigators reviewed 1270 scientific articles and analyzed 26 of them in depth, including seven RCTs and a 2016 systematic review and meta-analysis.

The authors make a "strong" recommendation, for the use of metformin as an "alternative first-line intervention" for antipsychotic drug-induced weight gain especially for patients for whom a lifestyle intervention is unacceptable or inappropriate. The guideline recommends starting Metformin early for patients who gain more than 7% of their baseline weight within the first month of antipsychotic treatment. It also endorses metformin when weight gain is established.

Vitamin C Fares Poorly in Latest Septic Shock Trial

More patients in septic shock who received vitamin C infusions died or experienced greater organ dysfunction than those who received placebo - according an article published in NEJM. This unexpected finding has mystified experts in the field as the anti-oxidative properties of vitamin C, have been thought to help protect organs from damage caused by oxidation in patients who go into septic shock. (Two smaller studies earlier had found that vitamin C was beneficial).

In the LOVIT study, which was a randomized placebo-controlled trial of 863 patients in Canada, New Zealand, France, and other countries, 429 patients were randomly assigned to receive a vitamin C infusion every 6 hours for 4 days, and 434 were assigned to receive placebo. At baseline, almost all patients had received vasopressor infusion. At 28 days, 191 of 429 patients (44.5%) in the vitamin C group had died or had persistent organ dysfunction, compared to 167 of 434 (38.5%) in the placebo group. The findings throw into doubt the use of vitamin C for people with sepsis.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Minocycline	Agranulocytosis
2.	Fingolimod	Liver Injury
3.	Erenumab	Hypertension
4.	Ivermectin	Encephalopathy
5.	Tinidazole	Fixed Eruption
6.	Sertraline	Microscopic Colitis

Drug Information Centre: An Overview

Drug Information Centres (DIC) play a significant role in the healthcare system as they offer unbiased and up-to-date information. Drug Information Centres hold a unique place in the healthcare system as the best sources of scientific data for users to access through the accessible databases in order to get the information they need to solve a problem or meet a particular requirement. Providing information to the public or to other healthcare professionals is the focus of a drug information centre, which can be run by pharmacists or other healthcare experts. The drug information centre offers trustworthy, unbiased information to medical professionals, gives patients and consumers individualised counselling and health information, and tracks and records adverse medication reactions. The Pan American Health Organization (PAHO) defines "Drug Information Centres (DIC) as operational units that provide technical and scientific information about drugs in an objective and timely manner". In order to serve as a source of curated, thorough medication information, the first drug information centre was established in 1962 at the university of Kentucky medical centre. A drug information centre can also support clinical research, drug use reviews, health education initiatives, and pharmacovigilance (the reporting of adverse medication reactions).

Objectives of DIC:

1). To encourage pharmacists, doctors, and other healthcare workers to use medication information resources effectively.
2). To give medical students the knowledge they need to be knowledgeable drug information specialists.
3). To address the practitioners' needs for drug information by offering an organized resource of specialized data on medication therapies.
4). To broaden the healthcare provider's responsibilities in the hospital and neighbourhood by offering drug information services.
5). To encourage the adoption of rational drug therapy for patients by enhancing the accessibility and efficiency of pharmacological information.

Types of Drug Information Centers (DIC):

1). Hospital-based: The information centre is housed inside the hospital and handles tasks like responding to patient questions, helping with formulary decisions, taking part in drug evaluations, coordinating the reporting of adverse drug reactions, publishing newsletters, offering in-service training, supporting pharmacy and therapeutic committees (PTC), and keeping an eye on investigational drug activity.
2). Industry-based: DIC in the industry has access to all of the specific information gathered since a medicine was first created. They have access to pertinent expertise, the code to all published publications, and knowledge of unpublished documents.
3). Community-based: Information centres with information regarding drug-related national programmes currently being run in the nation are situated at the community level, which aids in raising public awareness.

Requirement to set-up Drug Information Centre in hospital:

1. **Equipments:** Telephone, Computers, Fax machine, Printer, and Copier machine.
2. **Specific Area:**
   a). It should be close or inside the pharmacology department to allow both pharmacology staff and other healthcare providers to reach it easily.
   b). A sign or label on the door to specify who will be allowed to enter the DIC room

3. **Personal:**
   a). **Specific Criteria:** The person working in the DIC should hold valid degree like MD/MBBS with PhD/MSc with PhD in a medical college with specialized training in drug information center and minimum experience of 1-2 years.
   b). **General Criteria:** Computers skills and the person should be cooperative, confident, accurate, good English language
4. **Resources:**
   a). Primary resources (scientific journals, thesis, etc.)
   b). Secondary Resources (Review articles, hand books, text books, etc.)
   c). Tertiary Resources (Dictionaries, Encyclopedia, Pharmacopoeia, etc.)

Systematic Method for Responding to Drug Information Requests:

1). Take into account the requester's educational background and professional or experiential history.
2). Determine needs by posing probing inquiries or by looking at the medical file to determine the real issue. Determine how urgent a reaction is needed.
3). To help with scenario analysis and resource selection, categories inquiries as being patient-specific or not, as well as by the type of query.
4). Gather more thorough background information, such as patient information, to tailor the response to the needs of the patient, their relatives, or healthcare professionals.
5). Conduct a thorough literature search by choosing relevant articles from the primary, secondary, and tertiary literature.
6). Analyze, combine, and evaluate data from various sources. As a result of the information given, more information requirements should be anticipated.
7). As required by the requester and as suitable for the circumstance, respond by written or oral consultation, or both.
8). Conduct a follow-up evaluation to analyze the patient's outcomes and the usefulness of the information given.
9). As necessary, record the request, information sources, answer, and follow-up.

Quality Assessment:

For maximum clinical utility and to establish the veracity of the provided information, responses to requests for drug information should be accurate, thorough, and prompt. It is possible to choose which types of patient-specific requests, how many requests there are at random, and for how long to evaluate the quality of the responses.

Conclusion:

Since they offer unbiased and up-to-date information, Drug Information Centres (DIC) play a significant role in the healthcare system. The future of drug information centres in India depends on the level of service, perceived legitimacy among clients, and assessment of development. Although it was not possible to compare the same variables for all DIC, it was clear that they engaged in more than just responding to consultations. They also produced bulletins, participated in pharmacy and therapeutics committees, and engaged in a variety of other activities. The concept and purposes of the DIC are found to be universal beyond national boundaries.

New Drug Approvals…

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of Type 2 DM. The recommended dose is 2.5 mg- 15 mg/weekly SC.

Oteseconazole is an oral azole antifungal drug approved to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are not of reproductive potential. The recommended dose is 600 mg orally on day one followed by 450 mg orally on day 2 and then from day 14- 150 mg orally per week for 11 weeks.

Mavacamten is a cardiac myosin inhibitor approved for the treatment of NYHA class II-III obstructive hypertrophic cardiomyopathy (HCM). The recommended dose is 2.5 mg - 15 mg /day orally.

Ganaxolone is a GABA A receptor modulator approved for the seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD). The recommended dose is 150 mg – 600 mg TID orally.

Cartoon Corner…

Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

GUEST COLUMN:

Drug abuse through Forensic lens: Role of Forensic Pharmacololgy and Forensic pharmacovigilance

The world is witnessing a rapid growth of drug abusers, who had started using drugs either to experiment or out of curiosity or due to peer pressure. It not only affects the individual but also his family, friends, and society – physically, socially and financially. This has led to an increased incidence of criminal and civil litigations. The skills and expertise of a forensic expert with knowledge about drugs and chemicals can be useful in solving a diverse number of legal cases.

Role of Forensic Expert in Drug Abuse cases:

In the court of law, crimes which are committed under the influence of a drug are the most frequently reported ones. These could be because of drug resulting in behavioral change or thought process of the person. These substances are frequently at issue in criminal and civil cases involving homicide, drug overdoses, and cases involving personal injury and auto accidents. Also, their actions and addiction liability have profound medico-legal implications.

During an investigation, forensic experts must testify and clearly explain questions relating to the association of drugs/substances with an individual's behavior, injury, illness, or death. Invariably they will be asked to interpret the effects of drugs, and their duration of action concerning medico-legal issues.

Alcohol and other drugs

Forensic expert can interpret the concentration of alcohol in the blood and its typical effects. Drug interactions, synergistic or antagonistic effect of different drugs on alcohol absorption or metabolism, and the disease state present in the individual can be assessed and provide great help to the judicial system.

Criminal cases

Drugs are invariably used during suicidal attempts or homicide, or sexual assault and forensic experts have to testify whether the use of such drug or poison can cause mental impairment or the use of a specific drug as the reason for criminal aggression.

Forensic Pharmacology:

There has been a continuous rise in medico-legal cases related to the use of drugs. This gives rise to various questions about the accuracy of the results obtained from the samples collected, the possibility to obtain the exact amount present at the time of death, the effect on the results due to the period elapsed since the death or the correlation of the results obtained from blood and different organs. This forms the basis of the involvement of the forensic expertise in the drug-related medico-legal cases, who is the right person to provide an accurate correlation between the body's drug concentration and any corresponding post-mortem alterations.

In India, clinical forensic medicine is neither well-developed nor implemented correctly; there is an inadequacy in providing proper medico-legal examination, accurate analysis, and appropriate documentation. In today's perspective, Forensic Medicine and Pharmacology must work in collaboration for high-quality and fast-paced medico-legal service in India. It is needed to accurately document and analyse the drug or chemical-related injuries of the victim and his or her body fluid samples. It can minimize the common errors occurring in emergency departments and hospitals. With the specialized workforce, errors in recognizing, collecting, or preserving evidential material, incorrect interpretations, or methods of investigation can be corrected.

To be qualified to provide an expert opinion in a court of law, an expert witness in a legal proceeding must have specialized knowledge, skills, experience, training, and even schooling. They are, therefore, needed to testify in court matters on different topics related to adverse drug reactions, medication errors, personal injury, drug testing, workman's compensation, impaired capacity, and driving under the influence of alcohol and poisoning.

Forensic Pharmacology discusses toxicities from the drugs in therapeutic use, commonly abused drugs, and drugs having no medicinal value. It deals with various laws on drugs, and schedules for procurement, manufacture, and distribution of drugs. Diverse new drugs are trouncing the markets with new molecules, claiming to contain “non-illegal” compounds but exhibit psychoactive effects called “smart drugs”.

There is an emerging trend to abuse existing drugs, so one needs to keep themselves updated with, their pharmacological or toxicological effects and guide the community and regulatory bodies with relation to potential drug abuse of these substances. Advances in analytical techniques have made the detection of drugs much easier which can help resolve medico-legal cases. Some drugs can alter the neurotransmitters and lead to poor impulse control and aggressive behavior. The role of a forensic expert becomes significant in this case because he/she is needed to testify to the truth of these claims.

Forensic pharmacovigilance:

Pharmacovigilance can be used in forensic cases like, e.g., establishing the effects of the drugs leading to crime (or) could this drug have caused this harmful effect on the person? Any injury or death in the form of adverse drug reactions that are caused by adulteration, or other substandard medicinal products which is identified by application of standard pharmacovigilance procedure is termed as “forensic pharmacovigilance”.

Conclusion:

In cases where corroboration cannot be made between the use of a drug with a specific associated outcome, it becomes difficult for judiciary to come to an appropriate conclusion. In such cases, a forensic expert can make a useful contribution by utilizing his or her knowledge of drug-related problems to provide relevant detail which help assist the legal system in taking the right decision.

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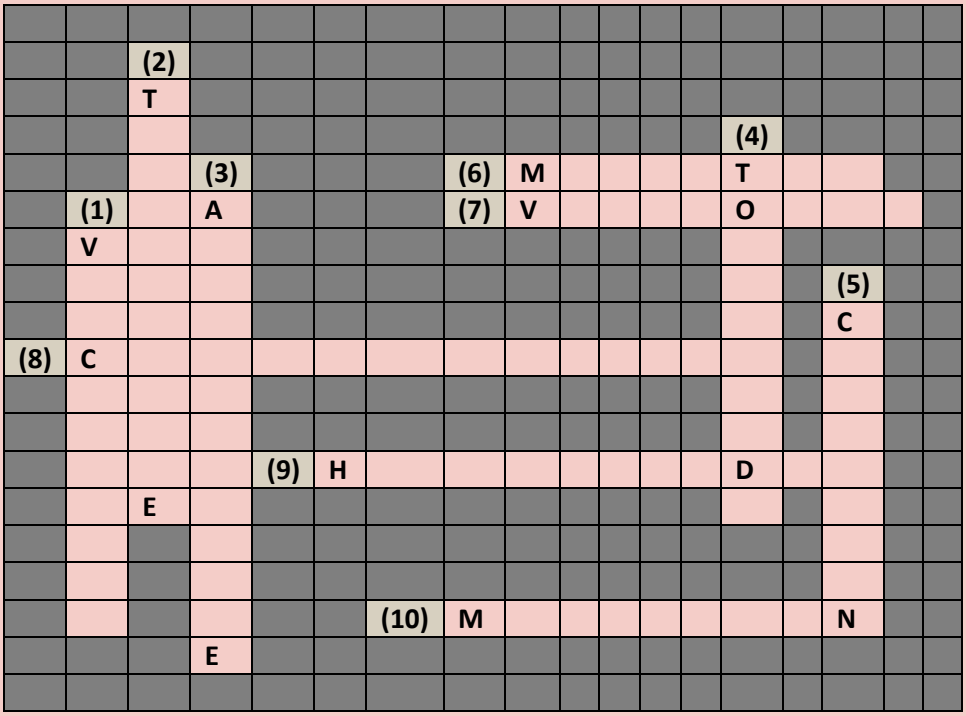

Downward	**Across**
1. Alkaloid obtained from Catharanthus roseus (11) 2. Antipsychotic drug belongs to Phenothiazines (12) 3. Tricyclic antidepressant acts by NA + 5-HT reuptake inhibition (13) 4. High ceiling diuretic (10) 5. Platinum based anticancer drug, very effective in metastatic gonadal malignancies (9)	6. Osmotic diuretic preferred in raised intracranial pressure/Intra –ocular pressure (*8*) 7. Broad spectrum anti-epileptic drug which acts by multiple mechanisms *(9)* 8. Anti-seizure drug which acts by blocking Na^+ channels *(13)* 9. Potent antipsychotic drug also preferred in Huntington's disease and Gilles de la Tourette's syndrome (*11)* *10.* Alkylating agent useful in multiple myeloma *(9)*

Quiz on Crossword Puzzle: *Drugs Causing Hyponatremia*

Click on the link below to access the quiz:

https://docs.google.com/forms/d/e/1FAIpQLSfVPlAHeeRnP8beLPuB5pAdMWD9zWIq9OP9RDfid7F3CQKleg/viewform?vc=0&c=0&w=1&flr=0

(Results and Winners of the Quiz will be announced in the next issue)