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Foreoword

In the Western Journal of Medicine January 2002 publication, they cited an anonymous composition about the history of medicine.

2001 BC Hear, eat this root.
1000 AD That root is heathen. Here, say this prayer.
1850 AD That prayer is superstition. Here, drink this potion.
1920 AD That potion is snake oil. Here, swallow this pill.
1945 AD That pill is ineffective. Here, take this penicillin.
1955 AD Oops, bugs mutated. Here, take this tetracycline.
1960 AD More mutations. Here, take next generation antibiotics.
2000 AD The bugs have won. Here, eat this root.

We may smile at this allegory. However, somewhere in between, we can deduce a timeless truth—the never-ending quest for knowledge and learning.

As physicians and healthcare workers, our search for wisdom and understanding should never end. Every patient that seeks consult in our clinics or being attended to on their sick beds adds to our clinical acumen and leaves us a piece of wisdom to learn.

Scheeropedia has been conceptualized to catch those learnings in a bulletin and share that wisdom with the rest of SMAH Bansha and the larger medical community.

Congratulations to the editorial and advisory board members who have made this publication possible. The collective knowledge in this piece of work will eventually translate to improvement in the quality of medical care we give to our patients and likewise, a contribution to the body of knowledge that can be of help to another colleague. Let us both learn from and contribute to Scheeropedia because the pursuit of knowledge is a lifelong endeavor.

Dr. Hector G. Gayares

Editorial

Drug bulletins are specialized periodicals providing comparative information and advice on the prescribing and use of medicines. Not only for the doctors but the drug bulletin will also be handy and effective to all health-care professionals, medical students and to some extent, the patients too.

Almost after 62 years of first drug bulletin- The Medical Letter on drugs and Therapeutics, published in USA and on about 62 year of establishment of Scheer Memorial Adventist Hospital (SMAH), here we publish the drug bulletin named “SMAH Drug and Therapeutics Bulletin”. We are planning to come up with quarterly issue of the drug bulletin to promote rational prescribing and keep medical fraternity up to date. Scheer Memorial Adventist Hospital has once again demonstrated that it is establishing itself as a "Centre of Excellence" in the nation's health system. Along with its holistic and all-inclusive state-of-the-art facility, the SMAH Drug & Therapeutics Bulletin has added to its distinction as one of the foremost in academic achievement and moving towards becoming one of the finest hospital in the country.

CHIEF EDITOR

Table of contents

Latest Research Updates	1-2
Drug Review: Clozapine	2-4
Plastic and Human Health	4-6
Overindulgence in Sugar and Gut Dysbiogenesis	6-8
Adverse Drug Reaction (ADR) Monitoring	9-11
Drugs Used in COVID-19	12-16

LATEST RESEARCH UPDATES

Bempedoic acid and cardiovascular outcomes in statin-intolerant patients

Date: April 13, 2023

Summary: Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain. By reducing the endogenous production of cholesterol, upstream of the rate-limiting enzyme HMG-CoA-reductase, i.e., the target of statins, bempedoic acid reduces circulating plasma concentrations of low-density lipoprotein cholesterol (LDL-C), and major adverse CVD events (MACE). Bempedoic acid has the potential to contribute to the reduction of CVD risk not only as monotherapy, but even further as part of a lipid-lowering combination therapy with ezetimibe, reducing LDL-C cholesterol up to 40%. Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization).

Source:Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJ,et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. New England Journal of Medicine. N Engl J Med 2023; 388:1353-1364

Sedentary time may significantly enlarge adolescents' heart

Date: April 12, 2023

Summary: In adolescents, sedentary time may increase heart size three times more than moderate-to-vigorous physical activity, a recent article concludes. The researchers explored the associations of sedentary time, light physical activity, and moderate-to-vigorous physical activity with cardiac structure and function. On average, adolescents who spent almost 8 hours/day sedentary and about 49 minutes/day in moderate-to-vigorous physical activity in the study showed higher left ventricular mass.

Source: University of Eastern Finland. "Sedentary time may significantly enlarge adolescents' heart." Science Daily. Accessed 12 April 2023.230412131217.html>.

Composition of joint lubricant potential culprit behind osteoarthritis

Date: April 11, 2023

Summary: The exact mechanism of cartilage breakdown in osteoarthritis is unknown, but damage from mechanical stress with insufficient self-repair is believed to be the main culprit. Researchers explore the disease-driven breakdown of hyaluronan and the mechanistic implications of these changes on the lubrication and subsequent wear of joints. The results showed low molecular weight hyaluronic acid, which mimics osteoarthritis-diseased joints, hinders the adsorption of the hyaluronic-acid-lipid complex. The lack of the formation of an amorphous film on the surface may reflect a consequence of osteoarthritis, since this film should help reduce friction and wear. The hypothesis is that the film's absence may increase wear of the cartilage surface. In contrast, high molecular weight hyaluronic-acid-lipid complexes form an amorphous film, which presumably helps maintain the mechanical integrity and longevity of efficient lubrication in healthy cartilage.

Source: Kangdi Sun, Tooba Shoaib, Mark W. Rutland, Joseph Beller, Changwoo Do, Rosa M. Espinosa-Marzal. Insight into the assembly of lipid-hyaluronan complexes in osteoarthritic conditions. *Biointerphases*, 2023; 18 (2): 021005

Lung adenocarcinoma promotion by air pollutants

Date: April 5 2023

Summary: More than 70 years ago, tumorigenesis was proposed to occur in a two-step process: an initiating step that induces mutations in healthy cells, followed by a promoter step that triggers cancer development. Environmental particulate matter measuring ≤2.5 μm (PM2.5), known to be associated with lung cancer risk, promotes lung cancer by acting on cells that harbour pre-existing oncogenic mutations in healthy lung tissue. Functional mouse models revealed that air pollutants cause an influx of macrophages into the lung and release of interleukin-1β. This process results in a progenitor-like cell state within EGFR mutant lung alveolar type II epithelial cells that fuels tumorigenesis.

Source: Hill, W., Lim, E.L., Weeden, C.E. *et al.* Lung adenocarcinoma promotion by air pollutants. *Nature* 616, 159–167 (2023). https://doi.org/10.1038/s41586-023-05874-3

Risk Factors Associated With Post−COVID-19 Condition

Date: March 23, 2023

Summary: Post−COVID-19 condition (PCC) is a complex heterogeneous disorder that has affected the lives of millions of people globally. Systematic review and meta-analysis of 41 studies including 8,60,783 patients found that female sex, older age, higher body mass index, smoking, preexisting comorbidities, and previous hospitalization or ICU admission were risk factors significantly associated with developing PCC, and that SARS-CoV-2 vaccination with 2 doses was associated with lower risk of PCC.

Source: Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post−COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med.* Published online March 23, 2023. doi:10.1001/jamainternmed.2023.0750

Overuse of Intravenous Proton Pump Inhibitors in General Medicine and Surgery Wards

Date: March 7 2023

Summary: Overuse of stress ulcer prophylaxis is prevalent globally despite guidelines leading to the added cost, especially the intravenous proton pump inhibitor (IVPPI). Overall prevalence of IVPPI use was 36.24% (274/756 admissions), in surgical ward, it was 39.45 (189/479) and in medicine ward, it was 30.68% (85/277). The mean age was 43.1 ±18.6 years. Inappropriate overuse in 253 (92.3%, significantly more in surgery-182 than medicine-7, p=0.001. Appropriate use was in 21 (7.7%, i.e., NPO-15, NPO + gastrointestinal bleed, and NPO + non steroid anti-inflammatory drugs each 3).

Source: Shah JN, Shah J, Sharma P, Shah J, Pandey A, Joshi C, Adhikari D, Gurung G, Khatri K, Basnet L, Shah S. Overuse of Intravenous Proton Pump Inhibitors in General Medicine and Surgery Wards. Journal of Nepal Health Research Council. 2022;20(3):570-6.

Putting anaesthetic emissions to bed: commitment on desflurane

Date*:* 03 March 2023

Summary*:* Desflurane, a volatile anaesthetic, used by anaesthetists has a global warming potential 2,500 times greater than carbon dioxide. Stopping the use of desflurane will reduce harmful emissions by around 40 kilotonnes of carbon a year – the same as powering 11,000 homes every year. Scotland is the first health service in the world to stop purchasing desflurane effective from March 2023, a high-carbon- footprint anaesthetic gas, for use in hospital theatres. Following the same footprint, the European Union has formulated a proposal to ban or at least severely restrict the use of desflurane starting January 2026.

Source:https://pharmaceuticaljournal.com/article/news/scotland-becomes-first-country-in-uk-to-stop-use-of-environmentally-harmful-desflurane

Drug Review: Clozapine

Almost 50 years ago, clozapine was initially developed as a possible therapy for the management of schizophrenia.[1] Less extrapyramidal symptoms (EPS) were noted to be induced by clozapine compared to other antipsychotics at the time, and it was also noted to have a significant analgesic potential.[1] Although it was the first atypical antipsychotic, it was not widely utilized and was taken off the market in the 1970s due to complaints of agranulocytosis. The drug was later reintroduced, and in 1990 it was given FDA approval as an antipsychotic in the United States.[1,2]

Clozapine's Impact on Neuropsychiatric Diseases The gold standard for treating schizophrenia and schizoaffective disorder when it is resistant to therapy is clozapine. While the possibility that a dopamine receptor blockade is a crucial part of treating schizophrenia, it is insufficient for the one-third of patients who are considered treatment-resistant and have a need for a clozapine trial. Clozapine has been discovered to have the lowest affinity of the currently available antipsychotics for the D2 receptor, but it is also known to block several other receptors, including the D4 and 5HT2A receptors, which may also contribute to its antipsychotic effects.However, its additional mechanisms of action, which distinguish it from other atypical antipsychotics, are not well understood.[1,2] Clozapine is now recommended by the International Society for Bipolar Disorders (ISBD) and the Canadian Network for Mood and Anxiety Therapies (CANMAT) as a third-line medication for the treatment of mania and as a potential adjuvant in maintenance treatments.[3] Clozapine does show some indication of success in the treatment of refractory mania, with or without psychotic symptoms, either given alone or as an additional medicine in their evaluation of off-label pharmacotherapies in treatment-resistant bipolar disorders.[4]

Adverse Effects[4-6]

Agranulocytosis: Patients who take clozapine run a 1% risk of developing agranulocytosis, which may be unrelated to dosage. Most cases require close monitoring

of blood absolute neutrophil counts since they typically arise early in the course of treatment, between six weeks and six months. Agranulocytosis is defined as having an ANC level below 500/mm, while neutropenia is defined as having an ANC level below 1500/mm.

a. **Myocarditis**: Less than 3% of patients who take clozapine get myocarditis as a side effect. The first four weeks of treatment are when patients experience this fatal, dose-independent side effect more frequently. Myocarditis symptoms in these patients can range from flu-like illness to respiratory and cardiovascular problems. With greater fatality rates, certain cases of clozapine-induced myocarditis may even appear atypically without any symptoms. Rapid drug titration, clozapine's metabolic adverse effects, concomitant use of selective serotonin reuptake inhibitors, and illegal drugs are all risk factors. Clozapine withdrawal is the first step in treatment, which could help the situation.
b. **Metabolic Syndrome:** Due to increased insulin resistance, clozapine is linked to considerable weight gain, type 2 diabetes, diabetic ketoacidosis, and elevated lipid levels. Due to their high affinity for serotonin 5-HT2C receptors, clozapine and olanzapine both have more metabolic adverse effects than the other atypical and standard antipsychotics. It is crucial to remember that the development of metabolic syndrome may also be influenced by other variables, such as a poor diet and a sedentary lifestyle. The metabolic syndrome is characterized by excess weight, dyslipidemia, elevated blood pressure, enhanced glucose intolerance, and elevated proinflammatory and prothrombotic states, according to the American Heart Association. One of the more dangerous side effects of clozapine is the emergence of DKA, which has a greater fatality rate than agranulocytosis. In order to lessen the metabolic effects of clozapine, recommendations include giving the patient advice on correct food, exercise, and other medications like metformin and orlistat.
c. **Seizures**: Both patients with epilepsy and healthy persons may experience a reduced seizure threshold after taking clozapine. The risk is often dose-dependent and ranges from 1% to 6%, especially with rapid titration. Younger patients may be at higher risk. Any stage of the therapy process may experience this side effect. An anti-epileptic like valproic acid may be helpful for those who take clozapine and develop a seizure.
d. **Excessive Salivation:** Sialorrhea is a benign disorder that is dose-dependent but may irritate some people. Aspiration pneumonia is one risk associated with excessive salivation.
e. **Pulmonary Embolism:** Clozapine is the only antipsychotic known to increase platelet adhesion and aggregation, according to a recent study comparing it to a number of other antipsychotics. Pregnant women and older patients who are taking high doses appear to be at greater risk. Several investigations have discovered this connection to be very deadly, dose-independent, and to show early onset.
f. **Constipation**: Clozapine's cholinergic and serotonergic effects on the digestive system can cause constipation or even ileus. One of the most frequent side effects of clozapine is constipation, which can affect 15% to 60% of all individuals taking it and is dose-dependent. In extreme circumstances, constipation can develop into ileus, which causes intestinal obstruction and ischemia. According to one study, these cholinergic effects may even cause dysphagia, which can develop into aspiration pneumonia. This implies that gastric hypomotility may not just affect the intestine. Ample hydration, the use of laxatives or docusates, and dose reduction are all components of management.
g. **Other:** Orthostatic hypotension, drowsiness, tachycardia, sexual dysfunction, and urine retention are possible additional adverse effects.

Dosing

Oral or intramuscular administration of clozapine are both options. The following strengths of clozapine are offered as oral tablets, oral disintegrating tablets, and oral suspension. The preferred dosage type is determined by the patient's acceptance and tolerance.[3,5]

a. 25 mg, 50 mg, 100 mg, and 200 mg of oral tablets
b. Doses of 12.5 mg, 25 mg, 100 mg, 150 mg, and 200 mg as orally disintegrating tablets
c. 50 mg/mL oral suspension dose (100 mL)

The FDA states that the highest daily dose of clozapine is up to 900 mg. For women, the typical dose is 300 mg, while for men it is 400 mg. The manufacturer advises starting clozapine therapy with dosages ranging from 25 to 75 mg/day given in two or three separate doses, followed by titration in increments of 25 to 50 mg/day to reach the target dose of 300 to 450 mg/day after two weeks. Up to twice a week, the dosage should then be increased by an additional 100 mg/day, up to a daily maximum of 900 mg. [4,5]

Contraindications:

Those who have experienced severe hypersensitivity responses to clozapine or any other ingredient in the formulation should not use clozapine. The following Black Box warnings are provided by FDA: Orthostatic hypotension, Neutropenia (owing to the possibility of agranulocytosis), Seizures, Myocarditis, Dementia (risk of a cardiovascular event).[7] Antifungals, oral contraceptives, fluvoxamine, ciprofloxacin, caffeine and disulfiram are just a few of the medications that may block cytochrome CYP1A2 and cause clozapine levels to rise. Among the medications that can cause CYP1A2 include omeprazole, rifampicin, cigarettes, phenytoin, and phenobarbital. The levels of the drug clozapine may also be impacted by additional medications that both activate (carbamazepine and rifampicin) and inhibit (cimetidine and erythromycin, among others) CYP3. The

metabolism of clozapine by CYP1A2 may be affected by tobacco, thus it's critical to comprehend how clozapine affects a patient's blood levels and effectiveness when they smoke or cease smoking suddenly.[6,8]

Monitoring:

Weekly haematological surveillance is required for the first 18 weeks of clozapine therapy due to the ongoing risk of agranulocytosis; after that, monthly monitoring is deemed sufficient.[7] In addition to being contraindicated in individuals with severe CNS depression, myeloproliferative diseases, or agranulocytosis, clozapine should also not be used with other medications that have the potential to affect bone marrow function or cause agranulocytosis.[8] Severe negative effects that need to be watched for include but are not restricted to:[7,8]

1. Agranulocytosis- ANC levels are determined by a complete blood count (CBC) every week. Neutropenia is indicated by ANC levels less than 1500/mm. Agranulocytosis is indicated by levels fewer than 500/mm. For the first six months, a complete blood count should be performed every week. The following six months, it should be done every other week. There is a national register in existence to oversee safe usage.
2. Metabolic Syndrome- Exercise, diet, and blood sugar levels.
3. Cardiovascular- Baseline troponin I or T levels, high sensitivity CRP levels, echocardiography, and BNP levels, as well as vitals and weekly laboratory testing of troponins, CRP, and BNP levels
4. Seizure- EEG and blood levels of clozapine

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Plastics and Human Health

Everyday, people are exposed to microplastics (MPs). Microplastics describes the entirety of all synthetic plastics and their products, which are smaller than 5 micro metre in size and which are either released directly into the environment or formed indirectly in the environment.[1] These microscopic (1–5000 µm) particles are constantly present in our food, water, beverages, and the air.[2] The first detection of MP in human faeces demonstrates that these particles can enter the body through the GI tract and are in fact consumed. Concerns have been raised about the influence on human health and the actual exposure. Although it is generally acknowledged that humans are exposed to MPs, little is known about the worldwide size, uncertainty, and variability of MP exposure concentrations and ingestion rates. Regarding the possible threats that MPs may bring to human health, these ambiguities have given rise to numerous controversies.[1] Aside from exposure, previous studies have not focused on and have largely ignored the destiny and transport of ingested MPs in the human body, which include intestinal absorption and biliary excretion. MP buildup in bodily tissues has been linked to immunological responses, oxidative stress, inflammation, and physical stress and injury. Studies looking at how MPs affect human cells have so far shown scant indication of a negative influence on cell viability.[1-3] The range of exposure concentrations employed in these investigations may not, however, be a true representation of the MP deposited in body tissues. Chemical toxicity is a potential risk associated with MP exposure.[3,4] Furthermore, it's possible that MPs present in foods like salt and seafood have absorbed toxins from the environment in which they were raised. The significance of MPs in influencing human exposure to chemicals has been hotly contested. Just a 100% leaching of the compounds from the particles was taken into account in previous investigations. Although being a plausible worst-case scenario, this is not the case because of the

kinetic restrictions and short gut residence times that make just a portion of the chemicals in the particles bioavailable. These chemical substances can also enter the body indirectly through direct food consumption or breathing. While carcinogenic compounds lack a dosage threshold level, some of these substances would still pose a risk if overall concentrations were higher than their threshold effect concentrations.[5,6]

Types of microplastics[7]

1. Primary microplastics type A categorizes and regards microplastics as a chemical. This category includes the types that are added directly to products (e.g. personal care products, cleaning agents, paints, etc.). This proportion is already often replaced by water soluble polymers ("liquid microplastics"). Products are then often "advertised" with the addition "free of microplastics" or "without microplastics".
2. Primary microplastics type B includes plastic particles that are created through the use of plastic products and that are directly (without detours) released into the environment as microplastics.
3. Secondary microplastics include all microplastic particles that are formed in the environment as a result of the slow decay of large plastic parts. This can happen through all kinds of external influences, e.g. through the influence of UV rays, bacteria or friction.

Detrimental effects of plastics on human health

The majority of polymers, like polyethylene (PE) and polypropylene (PP), are typically regarded as biologically inert substances. Yet, it has been demonstrated that some of the monomers and oligomers utilized in plastic items can leach during use and then end up in people. Two frequently cited examples are styrene, used in the manufacturing of polystyrene (PS), which is frequently used in styrofoam packaging, and bisphenol A (BPA), a monomeric building component of polycarbonate (PC) but also utilized as an additive in other plastics. These two monomers may both be endocrine disruptive substances (EDCs).[8] BPA has consistently been found in urine, blood, breast milk, and tissue samples, making it one of the relatively few compounds connected to plastics. The main routes of exposure are thought to be inhalation, dermal contact, and ingestion. A growing body of research is showing that many other monomers, oligomers, and chemicals related to plastics can have negative effects on humans, with exposure being linked to things like reproductive abnormalities.[2,9]

Much study has been undertaken on particle toxicity of engineered nanoparticles (ENPs) and airborne particulate matter (PM), which demonstrates that air pollution with small particulates is highly connected with respiratory and cardiovascular disease. This may be due to the fraction below 2.5 µm being primarily retained in the lungs and having the ability to pass through respiratory barriers. Hence, the induction of oxidative stress and subsequent inflammation is the primary mechanism of particle toxicity.[9] Likewise, the production of reactive oxygen species has been demonstrated in two human cell lines following exposure to polyethylene and polystyrene particles; nevertheless, cell survival was unaffected. Genotoxicity, apoptosis, and necrosis are other possible biological reactions that could result in tissue damage, fibrosis, and carcinogenesis.[4,7-9]

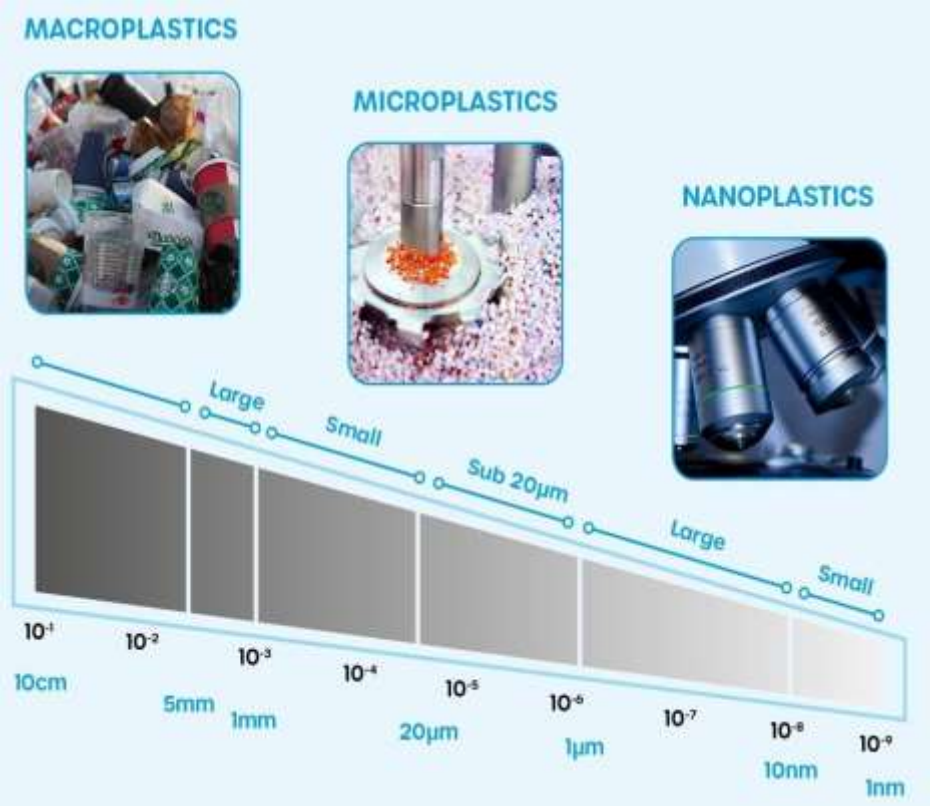

Figure 1: Different forms of plastics[7]

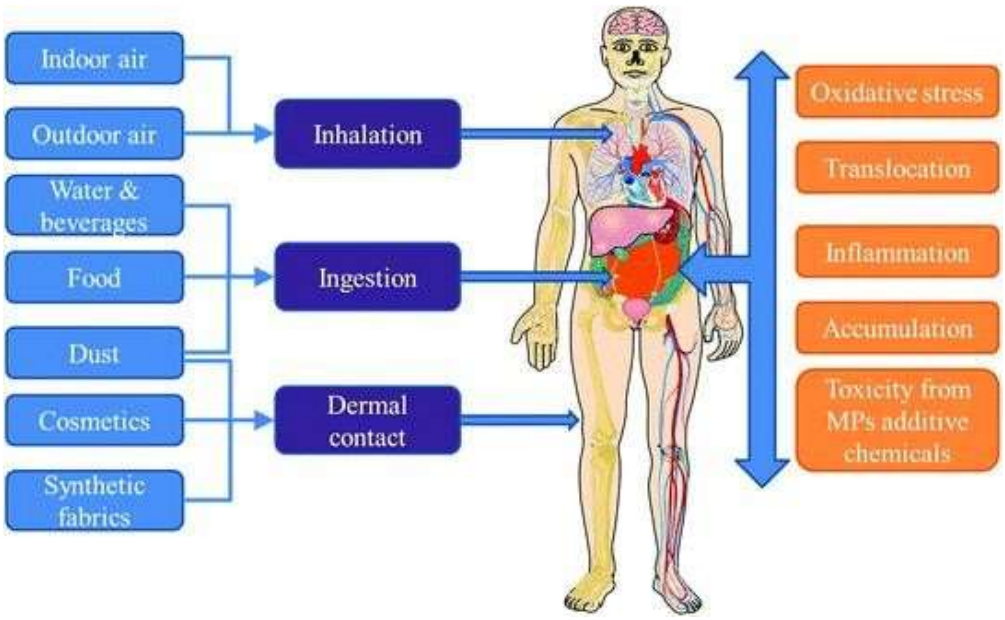

Figure 3: Pathways of human exposure to MPs and associated risks.[7-9]

Summary:

Due to their frequent discovery in all environmental compartments, microplastics (MPs) are a class of emerging pollutants that have drawn growing amounts of scientific and societal attention over the past ten years. Due to the potential harmful effects of MPs exposure, this is concerning and tiny MPs (<20 µm) can lead to inflammation and oxidative stress, whereas smaller MPs (<5 µm) can be taken up by cells and transported to accumulate in various organs.

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Overindulgence in sugar and gut dysbiosis

The gut microbiota is primarily modulated by diet, which is also linked to a number of disorders. It's significant that nutrition quickly and consistently changes the human gut flora. It is challenging to evaluate certain high-sugar diets since they frequently coincide with low fiber and high fat intake. Each nutrition type appears to have additive effects (for example, fructose plus high fat or sucrose plus high fat). Dietary additives common to Western human populations can affect the microbiota's ability to colonize the gut without necessarily acting as nutrients.[1] In terms of total carbohydrates, a change toward an enrichment in mucin-degrading bacteria that use the mucus layer as a source of nutrition results from the absence of fermentable fibers. The high fat and sugar content of the Western diet has been linked to a rise in the prevalence of chronic diseases such as obesity, type 2

diabetes, cardiovascular disease, and cancer. It has been shown via recent epidemiological and experimental investigations that a high-fat diet (HFD) can cause IBD.[2,3] Overindulgence in sugar is associated with an increase in the prevalence of noncommunicable diseases like diabetes, cardiovascular conditions, and cancer. By causing 35 million fatalities a year, this rising incidence is turning into a serious public health issue that is worse than infectious diseases.[4] The same health issues that excessive alcohol consumption can bring on can also be brought on by excessive intake of free sugars. Given that current consumption levels constitute sums that had no precedent during human evolution, many recent international recommendations have voiced worries about sugar intake in Westernized countries. The World Health Organization highly advises lowering free sugar intake in both adults and children to less than 10% of total energy intake, and even further lowering it to less than 5%.[5] Reduced diversity, increased Proteobacteria abundance, and decreased Bacteroidetes abundance are all microbial changes brought on by high dietary sugar levels. These changes are similar to microbiota dysbiosis linked to metabolic disorders, inflammatory bowel diseases (IBD), and other human disorders. Proteobacteria and other commensals that specialize in digesting complex carbohydrates and typically have slower growth rates may benefit from excess monosaccharides that are not absorbed in the small intestine at the expense of other commensals. As a result, excessive dietary sugar might be harmful in addition to giving out too much energy by altering the microbiota.[2,3]

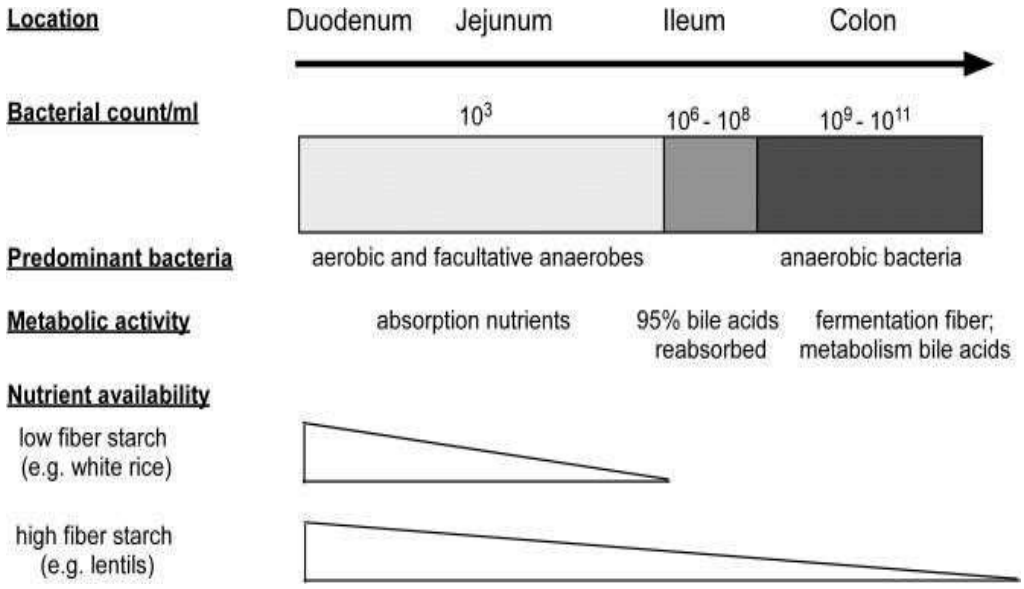

Figure 1: Shifts in the populations of gut bacteria[4]

Microbial ecology in gut and inflammation

Proteobacteria make up a small component of the normal gut microbiota, but if their numbers rise out of proportion, it could lead to generalized inflammation. The lipopolysaccharide (LPS, endotoxin) molecules carried by the phylum's class gamma-Proteobacteria and family Enterobacteriaceae are potent inflammatory response inducers. Interleukin 8 (IL-8) is a crucial chemokine responsible for triggering inflammatory responses.[6] When released from enterocytes, IL-8 transforms tight junctions and impairs epithelial integrity. Other gram-negative bacteria's LPS may not have as high pro-inflammatory capabilities as LPS of Bacteroides spp. because their structural makeup may be different from that of gamma-proteobacteria.[4,5,7] In a healthy adult's microbiota, Bacteroidetes and Firmicutes are the two bacterial phyla that are most prevalent. The main genus within the family Bacteroidetes, Bacteroides, is highly suited to the competitive gut environment and makes efficient use of complex polysaccharides generated from both hosts and plants. Despite the fact that the connection with the host is constantly context-dependent, the genus has been linked to a number of health advantages, including the downregulation of inflammatory responses in the gut. In vitro studies have demonstrated that Bacteroides spp. can inhibit the release of IL-8 from enterocytes in response to enterobacterial LPS, thereby attenuating inflammatory reactions and preserving the integrity of the enterocyte monolayer.[6,7] Acetate, butyrate, and propionate are the most prevalent short chain fatty acids (SCFAs) produced by the colon's bacteria during the fermentation of nondigestible carbohydrates. Diets rich in oligosaccharides modify the microbial composition, boost SCFA production, and lower luminal pH, all of which have an impact on the microbiota and SCFAs. SCFAs work as signaling molecules by activating AMP kinase and free fatty acid receptors 2 and 3, also known as G-protein coupled receptors 43 and 41, in addition to giving extra nutrients. SCFAs may offer protection against the onset of nonalcoholic fatty liver disease because they promote fatty acid oxidation while inhibiting de novo lipogenesis and lipolysis.[4] The balance between Proteobacteria and Bacteroidetes may contribute to the preservation of epithelial integrity and immunological homeostasis in the intestinal mucosa. By changing the

ratio of Proteobacteria and Bacteroidetes, high sugar intake appears to throw off the balance of the microbiota, causing them to have more pro-inflammatory traits, fewer immune-regulatory capabilities, and less ability to control epithelial integrity. In addition to the aforementioned changes in gut microbiota, a high-glucose or -fructose diet increased gut inflammation and permeability in rats.[8] More recently, it was discovered that a high-simple-sugar diet raised small intestine permeability in healthy adults as well.[9]

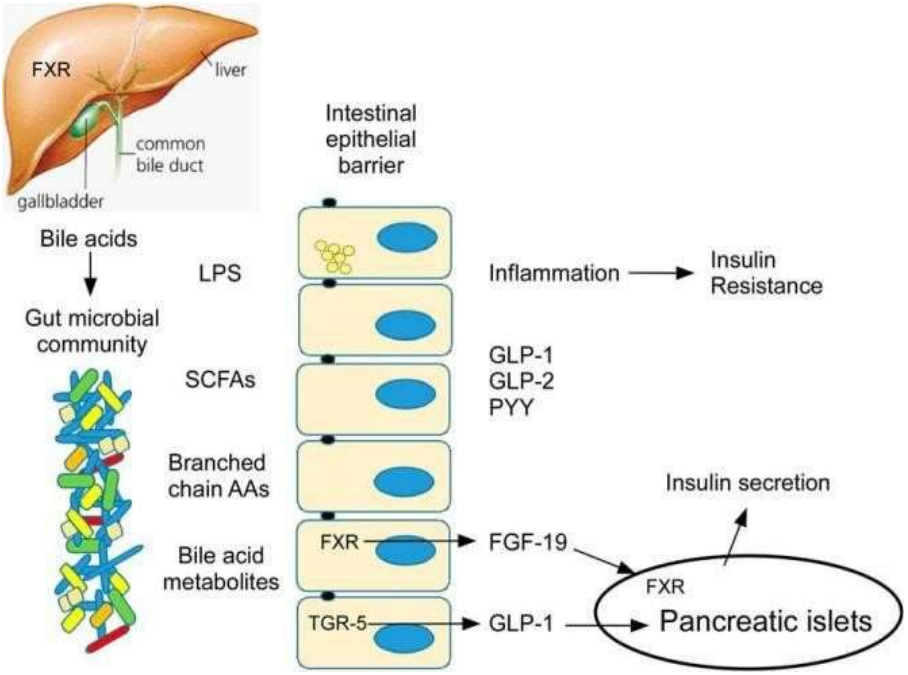

Figure 2: Possible processes relating the microbial ecology in the gut to glucose metabolism[4]

Summary:

Variations in microbial metabolism and community makeup along the digestive tract may be especially important for understanding metabolic disorders. In fact, small intestinal bacterial overgrowth is very common and may be the cause of obesity, diabetes, and nonalcoholic steatohepatitis. The upper GI tract undergoes complex carbohydrate and bile acid metabolism, which is often limited to the colon, in small intestinal bacterial overgrowth, resulting in early and enhanced absorption of SCFAs and deconjugated bile acids. Leaky tight junctions, bacterial translocation, and endotoxemia are additional effects of small intestine bacterial overgrowth.

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Adverse Drug Reaction (ADR) Monitoring in Nepal

World Health Organization (WHO) defines adverse drug reactions (ADRs) as noxious and unwanted effects produced by a drug, when it is applied for the ailment of disease or diagnosis.[1] A well-known fact is that no medication is completely free from side effects. The clinical trial and safety database of new drug are validated before the approval for marketing. It is essential to raise the awareness among patients and healthcare professionals regarding ADRs because many developed and developing nations are still facing the problem of ADRs. Pharmacovigilance has a number of functions, including the detection, observation, evaluation, and documentation of drug-related issues as well as the comprehension of the elements causing unfavorable effects.[2]

The main objective of ADRs monitoring is to disclose the quality and frequency of ADRs and to identify the risk factors associated with the adverse reactions. ADRs are also recognized as a reason for frequent hospital admissions causing heavy financial burden on hospitals. The purpose of hospital-based ADRs monitoring and reporting programs is to detect and quantify the hazards related to using medications supplied in a hospital environment.[4] Government of Nepal nominated Department of Drug Administration (DDA) in October 2004 as the focal point (National Pharmacovigilance centre) to liaison with WHO collaborating centre for International Drug Monitoring, Sweden and started collecting adverse drug reactions.[3] Nepal became a WHO programme member in July 2006. At present, there are 15 regional pharmacovigilance centers in Nepal.[3] These regional pharmacovigilance centers operate under DDA (DDA being the National centre for ADR monitoring). The regional centers report ADRs to the National centre (DDA) via 'Vigiflow' (an online program) which are then forwarded to the Uppsala Monitoring Center (UMC) by the National Centre.

Advantages of ADR surveillance

An ADR monitoring and reporting program provides details about the reliability and security of medicinal items that help for initiating the risk management plans. It assists in measuring the occurrence of ADRs and prevents the predictable harmful effects. Such program raises awareness of ADRs and educates the healthcare team, patients, pharmacists, and nurses about adverse drug reactions.

Types of Adverse Drug Reactions (ADRs)

The two main kinds of ADRs according to conventional pharmacological classification are type A (non-immunological, also known as intolerance), which is dose-dependent and predictable, and type B (immunological-allergic), which is unpredictable and not dose-dependent.[6] Around 85% of ADRs are type A (non-immunological), which are brought on by the drug's pharmacological action.[6] Although still widely quoted, this basic classification does not work for all ADRs, such as with chronic adverse effects associated with cumulative drug exposure (eg osteoporosis with long-term corticosteroids treatment) or withdrawal reactions (eg rebound hypertension with centrally-acting anti-hypertensive cessation). An alternative and perhaps more comprehensive classification scheme is 'DoTS', which classifies reactions dependent on the Dose of the drug, the Time course of the reaction and relevant Susceptibility factors (such as genetic, pathological and other biological differences).[6-8]

Incidence of ADRs

The frequency with which an adverse drug reaction (ADR) occurs is typically used to characterize its incidence. Very common, common, uncommon, rare, and very rare are the following:[7]

Table 2: Incidence of ADRs[7]

Risk descriptor	Happens to how many?		Percentage	
	From	To	From	To
Very common	1 in 10	or more	10	or more
Common	1 in 10	1 in 100	1	10
Uncommon	1 in 100	1 in 1,000	0.1	1
Rare	1 in 1,000	1 in 10,000	0.01	0.1
Very rare	1 in 10,000	1 in 100,000	0.001	0.01

Preventing adverse drug reactions

While some ADRs are unpredictable – such as anaphylaxis in a patient after one previous uneventful exposure to a penicillin-containing antibiotic – many are preventable with adequate foresight and monitoring. Preventability (or avoidability) usually refers to when the drug treatment plan is inconsistent with current evidence-based practice or is unrealistic when taking known circumstances into account. Epidemiological studies tend to find that between a third and a half of ADRs are (at least potentially) preventable although preventability is much easier to diagnose in hindsight. However, interventions that reduce the probability of an ADR occurring can be an important way to reduce the risk of patient harm. There are two basic steps that can be followed to prevent an ADR occurring:

a. Identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly.

b. Ensure the treatment plan mitigates any possible adverse effects.

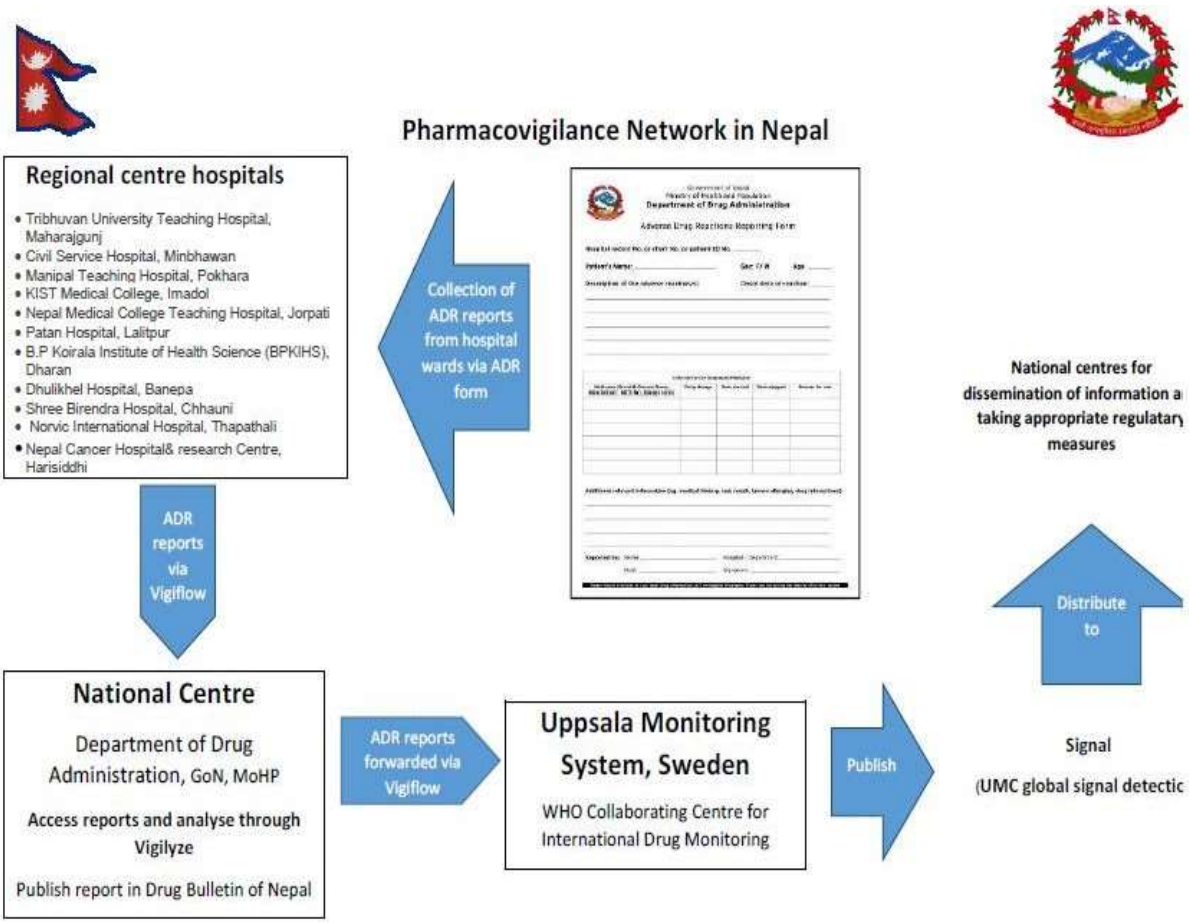


Figure 1: Pharmacovigilance network in Nepal[3]

Reporting of adverse drug reaction

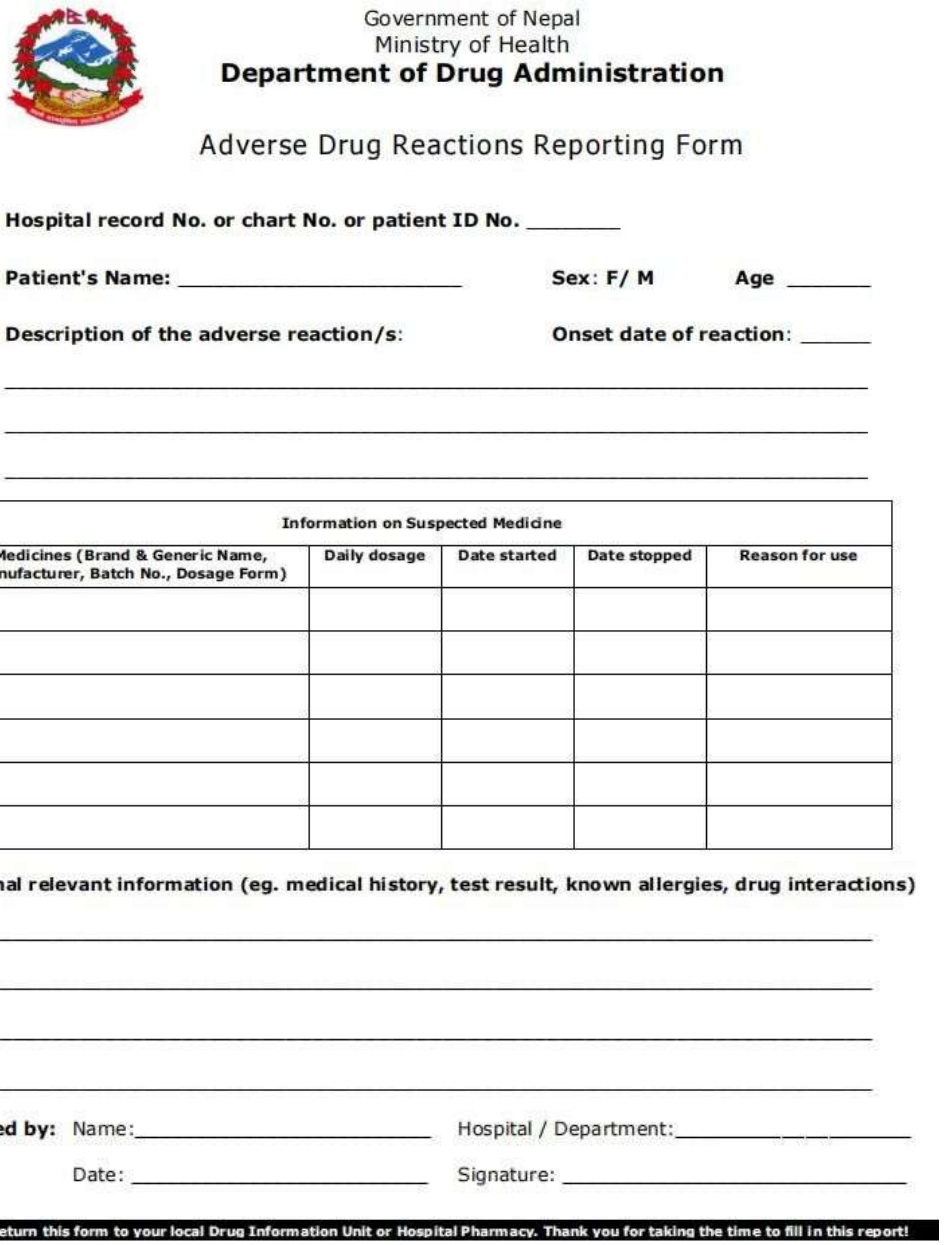
Spontaneous reporting systems, while widely adopted for pharmacovigilance, are most effective when the adverse events are rare and uncommon (less than 1% of treated patients) and when the event is typical of a drug-induced condition (eg erythema multiforme).[4,7] Their use is more limited in identifying a small increase in the rate of common events, such as myocardial infarction or stroke. This is the reason why recent drug safety scandals, such as thiazolidinedione-induced and rofecoxib-induced cardiovascular events, remained undetected despite widespread use of these agents. There are many other methods and data streams used in pharmacovigilance, including formal drug safety studies, published data, pharmaceutical company data from periodic safety update reports (PSURs) and shared international data. However, regulators and scientists are also looking at the ability of other 'big data' sources, such as social media, to detect early signals; this remains an exciting and largely unexplored area of research.[4-6]

ADR and causality assessment scales

It is ideal for ADRs to be impartially evaluated and presented using a reliable "Probability Scale." The Naranjo Probability Scale, the Uppsala Monitoring Centre (WHO-UMC), and the World Health Organization Collaborating Centre for International Drug Monitoring have all developed causality assessment systems that are widely accepted and used in clinical practice because of their straightforward methodologies.[8] The Naranjo Algorithm, or Adverse Drug Reaction Probability Scale, is a method by which to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores.[8] Because of its ease of use, the Naranjo ADR Probability Scale has become popular among doctors. The Naranjo scale also relies upon testing for drug levels, which is rarely helpful in idiosyncratic drug induced liver disease. The clinical-pharmacologic factors are taken into account by the WHO-UMC causality system, although prior awareness of the ADR is less important in this system.

Managing adverse drug reactions

Altering a dosage regimen or withdrawing a medicine suspected of causing an ADR are common methods of managing ADRs in practice.[5] However, the course taken to manage an ADR is likely to vary from clinician to clinician.



Government of Nepal
Ministry of Health
Department of Drug Administration

Adverse Drug Reactions Reporting Form

Hospital record No. or chart No. or patient ID No. _____

Patient's Name: _____ **Sex: F/ M** **Age** _____

Description of the adverse reaction/s: **Onset date of reaction:** _____

_____

_____

_____

Information on Suspected Medicine				
Medicines (Brand & Generic Name, Manufacturer, Batch No., Dosage Form)	**Daily dosage**	**Date started**	**Date stopped**	**Reason for use**

Additional relevant information (eg. medical history, test result, known allergies, drug interactions)

_____

_____

_____

_____

Reported by: Name:_____ Hospital / Department:_____

Date: _____ Signature: _____

Please return this form to your local Drug Information Unit or Hospital Pharmacy. Thank you for taking the time to fill in this report!

Figure 3: ADR reporting form[3]

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Drugs used in COVID-19

Novel pneumonia, which started in Wuhan, China, in late December 2019, expanded quickly and has been recognized as a global pandemic health emergency since March 11, 2020.[1] The 2019 novel coronavirus (2019-nCoV), also known as the severe acute respiratory syndrome coronavirus-2, has been identified as the pathogen responsible for the disease (SARS-CoV-2). The World Health Organization designated the illness as coronavirus disease-2019 (COVID- 2019) on February 11th, 2020. (WHO).[1] SARS-CoV-2 is a member of the Coronaviridae family of the order Nidovirales, a family of enclosed single-strand RNA viruses known as coronaviruses. The four genera of Alpha, Beta, Delta, and Gamma-Coronaviruses (CoVs) that affect the lower respiratory tract range in severity from moderate to serious. The severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus have been responsible for outbreaks of fatal human pneumonia since the turn of the century (MERS-CoV).[2] Four structural proteins are typically present in coronaviruses: the spike (S), envelope (E), membrane (M), and nucleocapsid (N). It is noteworthy that the S protein allows the virus to enter the host cell. The host protease cleaves it into two functional subunits, S1 and S2, which are in charge of attaching to the host cell and fusing the membrane of the viral cellular component, respectively. The SARS-CoV and SARS-CoV-2 process their S protein by using the cellular serine protease TMPRSS2 and subsequently interacting with angiotensin-converting enzyme two cellular (ACE2) receptors. Various CoVs recognize various proteases and entry receptors.

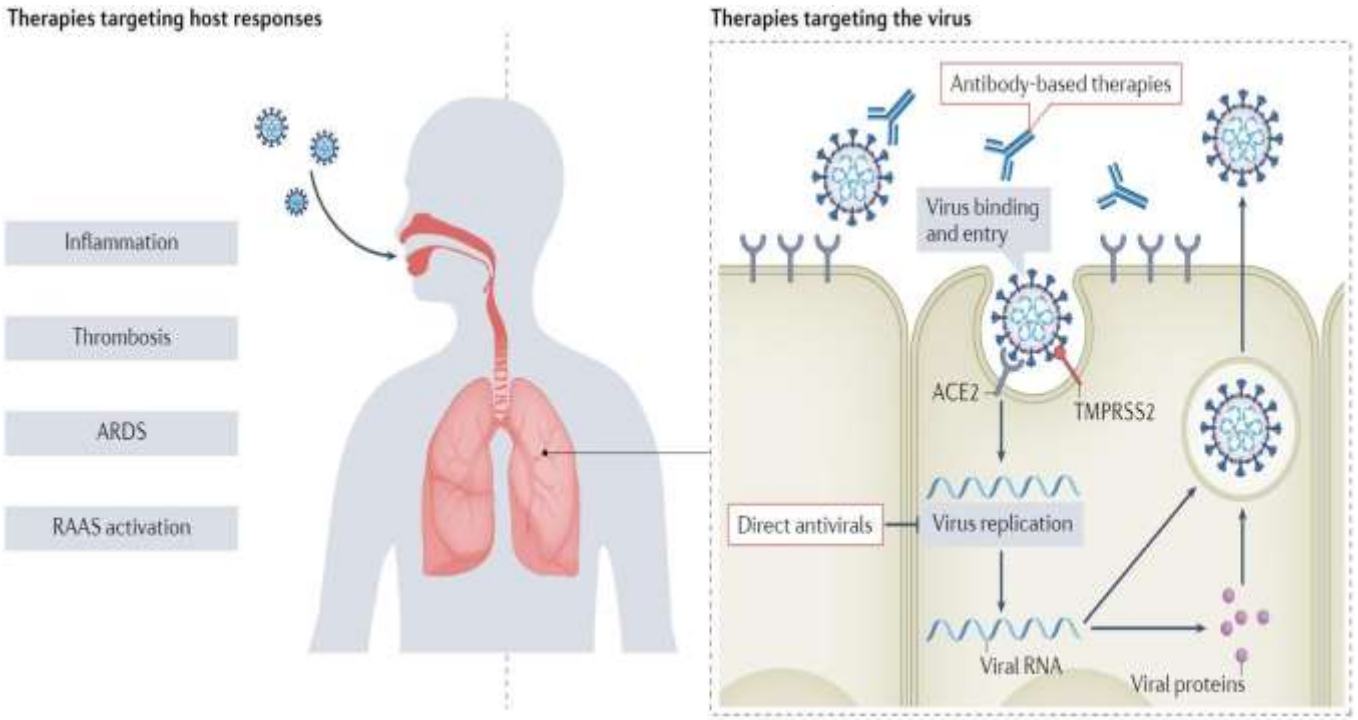

Figure 1: Classes of therapies for COVID-19

As prospective targets for pharmacological therapy against COVID-19, these viral components can be chosen which are as follows.[2-4]

a. SARS-COV-2 binds to the cell surface through ACE-II and Transmembrane serine protease 2 (TMPRSS2) cell membrane proteins (Entrance blocking drugs).
b. Virus enters to the cells through receptor mediated endocytosis and formation of endosomes,
c. Fusion of virus to endosomes leads to the genome releasing to the cytoplasm (Endosome fusion blocking agents),
d. Replication of the genome (Replication inhibitors),
e. Transcription of viral genes,
f. Translation of virus proteins (Virus proteins inhibitors),
g. Packaging the virus particles and,
h. Releasing the newly formed virus particles to the extracellular environment.
i. Cytokine storm and inflammatory mediators in the infection site leads to tissue damage (Inhibitors of inflammatory mediators).

j. Clot formation, as a secondary effect of COVID-19, is inhibited by heparins. Bradykinin receptor repressor inhibits plasma leakage to the lung tissue.

Table 1. List of Potential therapies for COVID-19[2,4,5]

Classification	Agent	Target	Treatment dosage	Approved for	Comments for COVID-19
Antiviral drugs	Darunavir	Protease inhibitor: inhibiting Gag-Pol polyprotein cleavage	800 mg daily	HIV	Positive effects in combination with other antivirals
	Oseltamivir	Neuraminidase inhibitor	75 mg twice a day	Influenza A and B	Ineffective
	Umifenovir	Hemagglutinin inhibitor	200 mg three times daily	Influenza A and B	No significant improvements
	Favipiravir	RdRp inhibitor	1600 mg twice daily on day 1 and 600 mg twice daily on days 2–14	Influenza	Symptoms reduction
	Remdesivir	RdRp inhibitor	200 mg/dose	Investigational drug	Authorized emergency use
	Ribavirin	Viral protein synthesis inhibitor	6 g over 12–18 h daily	Hepatitis C, Respiratory Syncytial Virus.	Effective as an add-on therapy
	Nafamostat and Camostat	Serine protease inhibitor	Nafamostat: 0.1–0.2 mg/kg/h of mixed with 5% DW Camostat: 2 × 100 mg pills 3 times daily for 5 days	Chronic pancreatitis, Anticoagulant in Japan	Improve patient's conditions effectively
	Lopinavir/ Ritonavir	Protease inhibitor, CYP4503A inhibitor	400 mg/100 mg; or 200 mg/50mg	HIV	Contradictory results
	Nelfinavir	Protease inhibitor	In vitro dosage: EC50 = 1.13, EC90 = 1.76 Upset	HIV	In vitro effectiveness with the IC50 of 1.3 μM
Antibacterials	Teicoplanin	Cathepsin L blocker	In vitro dosage: IC50 = 1.66	Treatment of bacterial infections.	In vitro effectiveness with the IC50 of 1.66 μM
	Azithromycin	RNA-dependent protein synthesis inhibitor	500 mg on day 1 followed by 250 mg once daily	Treatment of bacterial infections.	Effective through co-treatment with HCQ
Antimalarial agents	Chloroquine & hydroxychloro-quine	Lysosome inhibitor	CQ:600 mg base once on day 1 followed by 300 mg base once daily for a total treatment duration HQ: 800 mg once on day 1, followed by 400 mg/day as a single dose or in 2 divided doses	Malaria	Ineffective and clinical trials paused by FDA on 25 May 2020

Immunomodulators	Anakinra	Recombinant IL-1 Receptor antagonist	2 mg/kg/day (Max:100 mg/day) or 4mg/kg/day (Max:200 mg/day)	Rheumatoid arthritis	Effective compared to standard care
	Bamlanivimab	neutralizing IgG1 monoclonal antibody against the receptor-binding domain of SARS-CoV-2 spike protein, prevents viral attachment and entry of SARS-CoV-2	single dose aqueous solution vials in 700 mg/20 ml for intravenous infusion over 60 min	Emergency use authorization for COVID-19	Prompt administration of Bamlanivimab within ten days of symptom onset or following a positive test.
	Bevacizumab	Anti-VEGF	7.5 or 15 mg/kg IV.	Cancer	Second line treatment
	Sarilumab	IL-6 receptor inhibitor	200–400 mg/IV/ daily	Moderately to severely active RA	No improvement in outcomes
	Thalidomide	TNF-α suppressor	100 mg/day	Leprosy, Multiple myeloma	Patient's improvement effectively
	Tocilizumab	Interleukin 6 inhibitor	8 mg/kg, Maximum (800 mg/dose)	Rheumatoid arthritis, cytokine release syndrome	Contradictory results
	Interferon (α, β, λ)	Hindering the viral replication, the viral load reduction	The EC50 for IFN-α and IFN-β in vitro: 1.35 IU/ml and 0.76 IU/ml, respectively	Cancers, Autoimmune diseases, Hepatitis B and C	Significant reduction in viral replication and titer in combination with other therapies.
Angiotensin II receptor blocker	Losartan	Angiotensin II receptor blockade	15 mg/kg	Heart failure, hypertension	Attenuates lung injuries
Bradykinin B2 receptor antagonist	Icatibant	Target bradykinin, decreases the fluid extravasation and leukocyte recruitment to lung, which persists in pulmonary edema	30 mg injected s.c. every 6 h for three doses	Hereditary angioedema	Substantial reduction in oxygen supplementation with no serious adverse events
Corticosteroids	Dexamethasone	Anti-inflammation and anti-fibrotic agent	Dexamethasone 6 g/day Oral/IV	Natural corticosteroids, Inflammation, Autoimmune conditions, Allergy symptoms	Can be used in specific clinical conditions.
Anthelmintic	Ivermectin	IMP α/β1-mediated nuclear import inhibitor	600 μg/kg once daily	Parasitic infections	Effective in in vitro examinations and safe.
	Nitazoxanide	Antiprotozoal agent	500 mg every 6 h for 14 days	Treatment of various Helminths, Protozoal	Antiviral potential against MERS-CoV and other coronaviruses in in-vitro
Antiprotozoal	Emetine	Protein synthesis inhibitor: binds	In vitro dosage: EC50	Amoebiasis	Effective in in vitro with EC50 at 0.46 μM

		to ribosomal E site	= 0.46 μM		
H2 antagonist	Famotidine	Binds to papain like protease, and the SARS-CoV-2 genome may encode protease.	40 mg–60 mg 8hourly	Heartburn, GERD, and Zollinger-Ellison syndrome	An empty stomach along with other treatments
Anticoagulant	Heparin (LMWH)	Anti-thrombin	UFH 250 U/kg or LMWH 100 U/kg twice daily	Prophylaxis treatment for venous thrombosis, pulmonary embolism, and peripheral arterial embolism	Effective in combination with other therapies

Abbreviations-CYP3A: Cytochrome P4503A; RdRp: RNA-dependent RNA-polymerase; DW: dextrose water; EC50: half maximal effective concentration; IC50: half maximal inhibitory concentration; IMPα/β1: importin α/β1; U: unit; UFH: unfractionated heparin.

Vaccines

Besides the drugs, several vaccines are at administration stage worldwide of which mRNA-1273 (Moderna), BNT162b2 (BioNTech/Pfizer), ChAdOx1/AZD1222 (Oxford/AstraZeneca), JNJ-78436735/Ad26.COV2.S (Johnson & Johnson), Sputnik/Gam-Covid-Vac (Gamaleya), NVXCoV2373 (Novavax), BBIBP-CorV (Sinopharm), CoronaVac (SinoVac), and BB152/Covaxin (Bharat Biotech) vaccines are worth to note according to the registered trials as well as their effectiveness.[6] The majority of vaccines should provide protection against SARS-CoV-2 variants, particularly those found in the UK and South Africa and identified as K417N/T, E484K, and N501Y mutations. Based on their ability to trigger a reasonably wide humoral and cell-mediated immune response (within the receptor-binding domain), yet, if the variants become able to bypass host protection, the small alterations in SARS-CoV-2 are not even unlikely to make these vaccinations ineffective against COVID-19 mitigation. Some of the SARS-CoV-2 vaccines that have been developed from any of the platforms of inactivated/live attenuated viruses (NCT04412538 and NCT04324606, respectively), virus-coated or protein-subunit vaccines (representative trial NCT04405908), replicating/nonreplicating viral vectors (NCT04341389), DNA vaccines (NCT04368988), and RNA vaccines are currently being administered to the target population.[7] The creation of COVID-19 vaccines is moving along at a rapid pace in terms of research, design, and development. Amazingly, the entire process of developing a vaccine—including the necessary clinical trials—has been cut from 10-15 years to 15–18 months. As a result, beginning in 2021, many vaccinations are being marketed simultaneously. There are now 24 vaccines in phase 4 of research and approximately 164 candidate vaccines that are currently being developed.[8]

Table 2. COVID-19 Vaccines with WHO Emergency Use

S.N.	Vaccine	WHO EUL Holder	NRA of record	Date of EUL Recommendation
1	COMIRNATY® COVD-19 mRNA Vaccine (nucleoside modified)	BioNTech Manufacturing GmbH	European Medicines Agency (EMA)	31-Dec-20
			Food and Drug Administration (FDA)	16-Jul-21
3	VAXZEVRIA COVID-19 Vaccine (ChAdOx1-S [recombinant])	AstraZeneca AB	European Medicines Agency	15-Apr-21
			Ministry of Health, Labour and Welfare	9-Jul-21
			Therapeutic Goods Administration	21-Aug-21
			Health Canada	23-Dec-21
4	COVISHIELD™ COVID-19 Vaccine (ChAdOx1-S [recombinant])	Serum Institute of India Pvt. Ltd	Central Drugs Standard Control Organization (CDSCO)	15-Feb-21
5	COVID-19 Vaccine (Ad26.COV2-S [recombinant])	Janssen–Cilag International NV	EMA	12-Mar-21
7	SPIKEVAX COVID-19 mRNA	Moderna Biotech	EMA	30-Apr-21

	Vaccine (nucleoside modified)		Ministry of Food and Drug Safety (MFDS)	23-Dec-21
		ModernaTX, Inc	FDA	6-Aug-21
8	Inactivated COVID-19 Vaccine (Vero Cell)	Beijing Institute of Biological Products Co., Ltd. (BIBP)	National Medicinal Products Administration (NMPA)	7-May-21
9	CoronaVac COVID-19 Vaccine (Vero Cell), Inactivated	Sinovac Life Sciences Co., Ltd	NMPA	1-Jun-21
10	COVAXIN® Covid-19 vaccine (Whole Virion Inactivated Corona Virus vaccine)	Bharat Biotech International Ltd	CDSCO	3-Nov-21 Suspension of supply
11	COVOVAX™ COVID-19 vaccine (SARS-CoV-2 rS Protein Nanoparticle [Recombinant])	Serum Institute of India Pvt. Ltd	CDSCO	17-Dec-21
12	NUVAXOVID™ COVID-19 vaccine (SARS-CoV-2 rS [Recombinant, adjuvanted])	Novavax CZ a.s.	EMA	20-Dec-21
13	CONVIDECIA COVID-19 Vaccine (Ad5-nCoV-S [Recombinant])	CanSino Biologics Inc.	NMPA	19-May-22

Summary

The sole medication for which the WHO has granted permission for emergency use is remdesivir. Darunavir and Oseltamivir failed to improve and were declared ineffective. Importantly, although having beneficial therapeutic effects, the WHO limits the use of corticosteroids for certain comorbid illnesses, and the FDA additionally prohibits the use of chloroquine and hydroxychloroquine. On May 25, 2020, their clinical studies come to an end. Azithromycin and ribavirin are also mentioned as promising co-treatment and alternative therapy possibilities. This simultaneous combo is a great technique to quickly use several different pathways. A multivalent vaccine that replaces the current vaccine's spike protein with a modified molecule made of new amino acids or other novel molecule(s) may be effective against the new variants of SARS-CoV-2. Constant genomic analysis along with monitoring the host protective immunity against the new variety of the vaccine(s) against the emerging variants may improve designing new vaccines with the necessary modifications.

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Opportunity: We invite submission of articles, drug reviews, case reports, latest research updates, newer treatment guidelines, and personal viewpoints on medical treatments for second issue of SMAH DTB.

Please send your feedback, comments and articles to dtb.smah@gmail.com

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