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PHARMACOALERT
NEWSLETTER

Drug Safety Alert, New Drug Marketed, Drug Interactions And Banned Drugs

Contents

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From the Desk of Editorial Team

The department of Pharmacology, Dr. RMLIMS, Lucknow, is pleased to present the April issue of our newsletter. As we all are aware that the world is yet to tide over the pandemic, and scientists and research organisations around the world are in quest of potential treatments and vaccines for the new coronavirus disease (COVID-19), trying to turn to old molecules that are either out of production or those on which development work stopped due to lack of commercial viability; in order to slow the pandemic and lessen the disease's damage. As quoted by William Osler "Medicine is a science of uncertainty and an art of probability", we are yet to find a definitive cure for COVID-19. In view of these developments, in our current issue also, we have new relevant updates on the use of drugs and current status of vaccines in COVID-19 along with our regular features on Pharmacovigilance, Drug Safety Alert, New drug approvals and Medication Error.

The first section is dedicated to the Updates pertaining to Corona. This time we have tried to bring information regarding drugs which have caused concern in the scientific world regarding their use in COVID-19 in our article Drugs and Safety Concern of their use in COVID-19. Also, we have given information regarding the drug trials being undertaken in India and the different opinion of India and WHO regarding the use of Hydroxychloroquine in prophylaxis and treatment of COVID -19. Though each of these, information has been taken from authentic sources but due to the everchanging scenario and new information pouring in everyday, the information given may appear to be insignificant. Hope that you shall understand the situation and bear with us for any such inadvertent matter.

The Pharmacoalert editorial team is happy to receive feedback from our readers. It implies that the newsletter is making its impact in the mind of our readers. We are elated to have received suggestions for improvement and appreciation from our colleagues in the institute and outside. We feel extremely blessed and proud to share with you all the appreciation and love we received from one of the stalwarts in the field of Pharmacology Dr. K. K. Sharma.

Stay Safe and Keep Reading our Newsletter.

Message

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The ultimate aim of medical education is to produce not only health professionals who can fulfil the Good Clinical Care needs of the people in the community and the country but create resources that can propagate the same very process of medical education for the future generation of health professionals by creating new knowledge and skills by way of research. Approaches to imparting health education can be conventional through books, classroom and bed-side teaching in hospital wards but also by unconventional means. While former being a compulsory component, may at times bring a feeling of boredom by virtue of its binding nature, the later being non-compulsory maybe embraced by the receiver as one can avail it at leisure as and when its use is required.

The publication of News Letter like Pharmacoalert from a medical college giving a plethora of knowledge and new innovation in a variety of health and disease related areas with evidence-based information is an event which can be considered as non-conventional medium of reinforcing the medical knowledge and education. Actually, publication of a News Letter requires a lot of behind the stage planning and support from a variety of people from a number of departments of the medical school without whose active cooperation it cannot culminate into a successful venture.

Recently I came across the Pharmacoalert News Letter Special Fifth-COVID-19 Issue on a coveted WhatsApp group of young medical students and teachers of Pharmacology and cannot remain a mute reader but to highly appreciate not only the selection but also the tone and tenor of its quality content. It covered almost all aspects of the emergence of COVID-19 disease and its causative agent SARS-CoV-2 described in a succinct manner. True to its name linked to "Alert" it also alerted readers about the approval of new drugs in India and abroad, precision medicine and much needed effort to encourage Pharmacovigilance activity. The last one is a unique way to sensitize one and all to report on the drug/patient safety issues on the prescribed and consumed drugs.

My sincere prayers to the almighty to bless the Editorial team and its worthy patron, Dr A.K. Tripathi to give them new ideas, wisdom and success to continue this noble work of publication of the News Letter and improve upon the venture in the time to come.

(Dr K.K.Sharma)

Drugs and their Safety Concern in COVID-19

In this current SARS-CoV-2(COVID-19) pandemic, there is increased concerns in use of few drugs in COVID-19 patients with inconclusive evidences but warns to be cautious of the worsening of the symptoms.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs, and have a wide range of uses. Concerns have been raised that NSAIDs may be associated with an increased risk of adverse effects when used in patients with acute viral respiratory infections, including COVID-19. In a rapid systematic review, which was carried out on 20 March 2020 on NSAIDs and viral respiratory infections using MEDLINE, EMBASE, and WHO Global Database, the results showed very low certainty evidence on mortality among adults and children. Effects of NSAIDs on the risk for ischemic and haemorrhagic stroke and myocardial infarction in adults with acute respiratory infections are unclear. Moderate to high certainty evidence showed little or no difference between ibuprofen and acetaminophen (paracetamol) among children with fever with regard to effects on death from all causes, hospitalization for any cause, acute renal failure, and acute gastrointestinal bleeding. However, all these studies were concerned with acute viral respiratory infections or conditions commonly caused by respiratory viruses, but none specifically addressed COVID-19, SARS, or MERS.

Concerns exists that angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) increase susceptibility to coronavirus SARS CoV-2 (the viral agent that causes the disease COVID-19) and the likelihood of severe COVID-19 illness. These concerns are based on considerations of biological plausibility, and the observation that there is an overrepresentation of patients with hypertension and other cardiovascular comorbidities among patients with COVID-19 who have poor outcomes. Millions of people around the world are on treatment with ACE-Is and ARBs for hypertension, heart failure, coronary artery disease, or kidney disease. Speculation about worse outcomes among patients on these medications during the COVID-19 pandemic has caused widespread anxiety among patients and their care providers. On the other hand, the harms of indiscriminate withdrawal of these medications on cardiovascular outcomes are well documented. There is uncertain evidence that patients on long-term therapy with ACE inhibitors or ARBs are at higher risk of poor outcomes from COVID-19.

Also, there are controversies on reconsideration of use of antidiabetic medications. In an article by Cure et al., states that metformin increases lactate production with pre-existing increased lactate levels in COVID 19 infected patients due to cell destruction. However, SGLT2 inhibitors like Dapagliflozin lowers the lactate production and lowers the intracellular pH but may increase ACE2. Its known that COVID 19 penetrates to ACE2 at low pH, causing infection. But, when Dapagliflozin is combined with insulin treatment, insulin decreases ACE2 level by reducing ADAM17 activation and reduces viral load. Insulin also can prevent dapagliflozin from causing diabetic ketoacidosis, suggesting insulin and dapagliflozin combination to best treatment option in COVID 19 infection. However, dapagliflozin causes high risk of dehydration, acute kidney injury and diabetic ketoacidosis in these patients which raises serious concerns against the use of dapagliflozin.

Hydroxychloroquine and chloroquine have uncertain safety and efficacy data for treatment and prevention of COVID-19. Hydroxychloroquine and chloroquine can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. These risks may increase when these medicines are combined with other medicines known to prolong the QT interval, including the antibiotic azithromycin, which is also being used in some COVID-19 patients without FDA approval for this condition. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines.

To conclude, the existing literature does not currently provide conclusive evidence for or against the use of any drugs in the patients of COVID-19. However, judicious use of drugs should be done in benefit of the patient as per the safety concern being raised based on available evidence till date. With numerous clinical trials and experiments being conducted all over the world, more robust evidence can be anticipated in near future to take a well informed and evidence-based judgment for rational use of drugs in this pandemic.

DRUGS	Data from animal studies	Data from human studies	Concerns for use during COVID-19 pandemic
NSAIDS	Upregulation of ACE 2 by Ibuprofen		Caution has been raised due to upregulation of ACE however no direct evidence to support increased adverse drug reaction and poor outcome
ACE inhibitors/ ARBs	-	Upregulation of ACE 2 in hypertensives, Type 1 & 2 DM patients	Increased risk of poor outcome may be due to biological plausibility, however no direct evidence to support data of poor outcome due to increased ACE2 expression
METFORMIN	-	Increases lactate production	Theoretical risk of poor outcome, at low pH , increased penetration of COVID 19 virus expected due to increased lactate levels however, no data on human pulmonary ACE2 expression
INSULIN	Reduces renal ADAM-17 expression in diabetic mice thereby reducing urinary ACE2 shedding and increasing intrarenal ACE2 expression	-	No human data to support poor outcome. However, it is considered presently best treatment option in diabetic patients with COVID-19 infection.
Pioglitazone	Upregulation of ACE2 in insulin-sensitive tissues of rats	Downregulation of ADAM-17 in human skeletal muscles	Theoretical risk of poor outcome, however, no data on human pulmonary ACE2 expression
Liraglutide	Upregulates ACE2 in cardiac and pulmonary tissues of diabetic rats	-	Theoretical risk of poor outcome, however, no data on human pulmonary ACE2 expression
SGLT2 inhibitors	-	Promotion of renal ACE2 activity	Theoretical risk of poor outcome, however, no data on human pulmonary ACE2 expression
DPP4 inhibitors	$DPP4^{H/M}$ mice develops severe disease with MERS-CoV DPP4 inhibitors do not alter ACE2 activity in diabetic mice	DPP4 inhibitors might exert overall anti- inflammatory role	Theoretically, DPP4 modulation might help offset the cytokine- mediated acute respiratory complications of COVID-19

ACE2:Angiotensin converting enzyme; ADAM-17: A disintegrin and metalloproteinase-17; SGLT2: Sodium-glucose transporter 2; DPP4: Dipeptidyl peptidase 4; $DPP4^{H/M}$:Transgenic diabetic expressing human DPP4; MERS-CoV : Middle East Respiratory Syndrome-Coronavirus

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COVID-19 News Board

FAVIPIRAVIR AND UMIFENOVIR: UNDER TRIAL PROMISING DRUGS IN COVID-19

Trial permission for the antiviral drug Favipiravir grows hope for finding a potential treatment for COVID-19. Many trials are ongoing worldwide, meanwhile the *Indian pharma industry giants, Strides Pharmaceuticals and Glenmark Pharmaceuticals have received approval from the Drug Controller General of India to start clinical trials on Favipiravir in India*. The trials will not only be pooling to the worldwide data but also be beneficial in providing the first hand data for Indian population.

Glenmark has initiated phase 3 clinical trials of Favipiravir as a COVID-19 monotherapy option with 150 patients, enrolled from nine leading government and private hospitals across the country. So far, 30 patients have been randomized as reported till 26 May 2020.

Simultaneously, Glenmark has also got approval for starting trial for a combination of two anti-viral drugs, Favipiravir and Umifenovir, as a potential COVID-19 treatment. The study dubbed 'FAITH Trial' will look to enroll 158 hospitalized patients suffering from moderate COVID-19 infections in India. The study will examine whether early administration of a combination of Favipiravir and Umifenovir, both acting by different mechanisms, enhances antiviral efficacy on COVID-19 patients.

For the uninitiated, *Favipiravir* is an oral antiviral drug approved in Japan under brand name Avigan since 2014 for the treatment of novel or re-emerging influenza virus infections. It has a unique mechanism of action by which it inhibits viral replication: it is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and recognized as a substrate by viral RNA polymerase, thereby inhibiting RNA polymerase activity that is required for viral replication. Apart from influenza Virus it shows anti-viral activities against other RNA viruses such as arena viruses, bunya viruses and filo viruses. Thus, making it a potentially promising drug for specifically untreatable RNA viral infections.

Umifenovir is another oral antiviral drug licensed for the treatment and prophylaxis of influenza A and B infections in Russia and China Umifenovir impedes the viral attachment to cells and acts as a viral entry inhibitor. Additionally, it exhibits modulatory effects on the immune system and induces interferon-production. Hence a combined use of Favipiravir and Umifenovir acting on different mechanisms would offer a comprehensive antiviral cover on pre-entry and post-entry life-cycle of the SARS-CoV-2 virus.

It is expected that combining antiviral agents that have a good safety profile and act on different stages of viral life-cycle will prove to be an effective treatment approach to rapidly suppress initial high viral load and lead to overall improvement in clinical parameters.
Meanwhile Russia has granted Avifavir (known in Indian generics as Favipiravir) a temporary registration certificate to make it the first drug to be approved in Russia for COVID-19.

Do You Know?

On June 1, 2020, Central Drugs Standard Control Organization (CDSCO) has granted regulatory approval of Remdesivir for treatment of suspected or laboratory-confirmed coronavirus disease (Covid-19) in adults and children hospitalised with severe disease under "restricted emergency use" with condition for five dose administration. The estimated cost of 5 days treatment in India is 35000-42000 INR Vs. 3.4 lakh INR/$ 4460 in USA.

COVID-19 News Board

HYDROXYCHLOROQUINE BOON or BANE?

Who Suspends The Hydroxychloroquine Treatment Arm Of Study

Negative findings from largest study to date prompted the move

The World Health Organization has temporarily halted a large, international study of hydroxychloroquine for the treatment of Covid-19 due to new evidence linking the drug to an increased risk of death in hospitalized patients.

The largest international study published to date examining hydroxychloroquine and chloroquine in patients hospitalized with Covid-19 showed *use of both drugs to be associated with decreased in-hospital survival and increased frequency or ventricular arrhythmias*. Trial findings, published recently in The Lancet, also failed to confirm a benefit for hydroxychloroquine or chloroquine, when used alone or with a macrolide, on other in-hospital outcomes.

A team of investigators from the US and Switzerland, conducted the international registry analysis of the considered therapies among 96,032 SARS-CoV-2 confirmed patients hospitalized in 671 hospitals across 6 continents.

The patient population was split among 14,888 (15.5%) patients receiving treatment—1868 on chloroquine, 3783 on chloroquine plus macrolide, 3016 on hydroxychloroquine, and 6221 on hydroxychloroquine plus macrolide—and 81,144 serving as control, meaning they received none of these treatments.

Investigators excluded data from patients for whom one of the observed therapies was initiated >48 hours post-coronavirus diagnosis or while they were on mechanical ventilation, as well as those who received Remdesivir. They sought an outcome of in-hospital mortality and de-novo ventricular arrhythmias. The findings, which were comprised of 63,315 (65.9%) COVID-19 patients in North America, also indicated that greater patient BMI is associated with worse in-hospital survival rates.

On May 25, WHO officials announced that the hydroxychloroquine arm of the global Solidarity Trial would be paused due unfavorable early safety data from the trial

The WHO-led trial has so far recruited 3,500 patients from 17 countries, with the goal of including patients from 35 countries including India, to examine the safety and efficacy of various therapies being used for the treatment of patients with Covid-19. The registry included 671 hospitals on six continents, with data on 96,032 patients hospitalized between Dec. 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2.

The Solidarity Trial will continue to follow patients treated in other arms of study with the experimental drug Remdesivir, the combination antiviral treatments Lopinavir/Ritonavir, and the Cytokine IFN-β-1a.

Despite the safety warnings and discontinuation of HCQ study arm by WHO from Solidarity Trial, several countries including United States, Brazil, France have not made change in their authorization for the use of HCQ in COVID-19. Here in India also after the confusion caused by the WHO announcements ICMR stood by its revised expanded Guidelines for the use of Hydroxychloroquine which they have issued on 22nd May.

Just In

WHO has revoked the suspension and trials on Hydroxychloroquine shall resume as reported on 4th June 2020 and the above stated studies published have been retracted due to dubious data and study design.

REVISED ADVISORY ON THE USE OF HYDROXYCHLOROQUINE (HCQ) AS PROPHYLAXIS FOR COVID-19 INFECTION

The National Task force (NTF) for COVID-19 constituted by Indian Council of Medical Research reviewed and reported the data on the use of HCQ for the prophylaxis of SARS-CoV-2 infection among health care workers (HCWs).
The in-vitro testing of HCQ for antiviral efficacy showed reduction of infectivity / log reduction in viral RNA copy of SARs-CoV2.
The data from the Pharmacovigilance program of India, on safety profile of HCQ prophylaxis among HCWs indicated mild adverse effects such as nausea, abdominal pain, vomiting, hypoglycemia and cardio-vascular effects with few reports which were serious and showed prolongation of QT interval on ECG. In different studies it has been found that there is a significant dose-response relationship between the number of prophylactic doses taken and the frequency of occurrence of SARS- CoV-2 infection in symptomatic healthcare workers who were tested for SARS-CoV-2 infection. Amongst healthcare workers involved in COVID-19 care, those on HCQ prophylaxis were less likely to develop SARS-CoV-2 infection, compared to those who were not on it. The prophylactic use of HCQ is recommended as follows-

S. No.	Category of personnel	Dosage
1	Asymptomatic household contacts of laboratory confirmed cases	400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals
2	• All asymptomatic healthcare workers involved in containment and treatment of COVID-19 and asymptomatic healthcare workers working in non- COVID hospitals/non-COVID areas of COVID hospitals/blocks • Asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities	400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals *The experts further recommended for its use beyond 8 weeks on weekly dosage with strict monitoring of clinical and ECG parameters

- *The drug is contraindicated in persons with known case of:*
  1. *Retinopathy,*
  2. *Hypersensitivity to HCQ or 4-aminoquinoline compounds*
  3. *G6PD deficiency*
  4. *Pre-existing cardiomyopathy and cardiac rhythm disorders*
  5. *Children under 15 years of age and in pregnancy and lactation.*
- *The drug has to be given under strict medical supervision with an informed consent as it may rarely cause cardiovascular side effects such as cardiomyopathy and rhythm (heart rate) disorders and visual disturbance including blurring of vision which needs discontinuation of the drug.*
- *An ECG (with estimation of QT interval) may be done before prescribing HCQ prophylaxis and in those who are already on HCQ prophylaxis before continuing it beyond 8 weeks.*
- *An ECG should be done in case any new cardiovascular symptoms occurs (e.g., palpitations, chest pain, syncope) during the course of prophylaxis and at least one ECG should be done anytime during the course of prophylaxis even if its uneventful.*
- *The drug has to be given under strict medical supervision with an informed consent and a physician should be consulted for any adverse event or potential drug interaction before initiation of medication.*
- *The prophylactic use of HCQ to be coupled with the pharmacovigilance for adverse drug reactions through self-reporting using the Pharmacovigilance Program of India (PvPI) helpline/app (available at https://play.google.com/store/apps/details?id=com.vinfotech.suspectedadversedrugreaction&hl=en_I N)*
- *If anyone becomes symptomatic while on prophylaxis, he/she should immediately contact the health facility, get tested as per national guidelines and follow the standard treatment protocol and guidelines.*
- *All prescribed public health measures such as frequent washing of hands, respiratory etiquettes, keeping a distance of minimum 1meter and use of Personal protective gear (wherever applicable) should be followed, as the intake of this medicine should not instil a sense of false security.*

COVID-19 News Board

Is COVID-19 cure in sight with IVERMECTIN?

Bangladeshi Doctors Claim to Miraculously Treat COVID-19 Patients

A team of doctors from Bangladesh have given hope to entire world by staking claim that *Ivermectin in combination with Doxycycline can treat the Patients of COVID-19 with respiratory symptoms.* Few newspaper reports have also claimed the drug combination is being hailed as miraculous as it can turn positive patients into Corona negative within 72 hours.

While Scientists and researchers toil hard to find vaccine candidate and the results seem to come over by one or two years. Doctors world over are repurposing and trying old drugs in treating the Corona positive and COVID-19 patients. Many clinical trials are also being done on many already available drugs.

Taking lead, the doctors in Bangladesh have claimed that their research on the combination of two widely used drugs has yielded astounding results in curing the patients with acute symptoms of the coronavirus that has created havoc worldwide. Investigators informed that all of the patients have shown remarkable recovery being (COVID-19) negative in four days and 50 percent reduction of symptoms in three days after being treated with Ivermectin and Doxycycline.

Ivermectin has been used since 1980s, mainly in creams and lotions for head lice. Besides this, it is also used in a tablet form to cure roundworm infection and second-line treatment for scabies and rosacea, a skin condition that results in redness and causes pus-filled bumps on the face.

Earlier a study led by Monash University in Melbourne, Australia claimed that a single dose of the drug Ivermectin could stop the virus from growing in cell structure and informed that they found that even a single dose could essentially remove all viral RNA (effectively removed all genetic material of the virus) by 48 hours and even at 24 hours there was a really significant reduction in viral replication. While there is no clarity on how the drug functions, it appears to end the processes that allow proteins to move within the virus, these proteins would otherwise dampen the body's antiviral response, and allow the virus to replicate.

Doxycycline belongs to the Tetracyclines group of drugs which are highly lipophilic antibiotics that are known to chelate zinc compounds on matrix metalloproteinases (MMPs). Coronaviruses are also known to rely heavily on host MMPs for survival, cell infiltration, cell-to-cell adhesion, and replication, many of which have zinc as part of their MMP complex. It is possible that the zinc-chelating properties of tetracyclines may also aid in inhibiting COVID-19 infection in humans, limiting their ability to replicate within the host. Tetracyclines might also be able to inhibit RNA replication on positive-sense single-stranded RNA, like COVID-19.

After these positive reports, *Indian Council of Medical Research (ICMR), India's apex medical research body, is reviewing the benefits of drugs Ivermectin and Doxycycline as potential therapy for Covid-19.The Maharashtra task force has also permitted the use of the drug combination, and various hospitals in Mumbai have started to use in COVID-19 patients especially those with heart rhythm disorders.*

We hope that the present trend of success with Ivermectin and Doxycycline continues and we find a potential cure with these drugs as currently, there is a race against time to identify prophylactic and therapeutic treatments against COVID-19. Until these treatments are developed, tested, and mass produced, it might be prudent to look into existing therapies that could be effective against this virus.

COVID-19 Pandemic: Vaccine Development -Current Status?

Introduction

As the novel coronavirus pandemic persists across the world, researchers are working rapidly to produce a safe vaccine, which can help combat the COVID-19 disease caused by the SARS-CoV-2. More than 110 coronavirus vaccines are being developed globally with at least 10 candidates already in human trials. A vaccine would normally take years, if not decades, to develop. But in present scenario, researchers hope to achieve the same amount of work in just a few months.

Why is a coronavirus vaccine important?

The virus spreads easily and a majority of the world's population is still vulnerable to it. A vaccine is expected to provide protection by boosting the immune systems to fight the virus so that they do not get infected or afflicted with the disease.

How soon can the world expect a Covid-19 Vaccine?

Most experts opine a vaccine for COVID-19 is likely to become available for commercial sales by mid-2021. However, the pharmaceutical companies are racing to become first in delivering a safe and effective vaccine.

US company Moderna's mRNA-1273 and CanSino Bio's Ad5-nCoV, showed promising results in early trials and Chinese biopharmaceutical company Sinovac Biotech claimed that it is 99% sure that their Covid-19 vaccine will work, there is hope that we might have a vaccine by the end of this year. Also, many companies have claimed that by the end of 2020 they shall be able to develop a vaccine and they have already scaled up for the mass production to keep up with the huge demand.

Global vaccine development efforts: Current Status

Vaccine development efforts are being spearheaded by the Coalition for Epidemic Preparedness Innovations (CEPI), headquartered in Oslo, Norway. CEPI is a global partnership that was specifically set-up to develop vaccines in health emergencies such as the present pandemic. More than 110 coronavirus vaccines are being developed globally with at least 10 candidates already in human trials. According to WHO, seven vaccines had entered human trials as of 23 April, and 77 others were in development. The vast majority of these vaccines use the modern tools of genetic engineering.

Vaccine Platforms

- **Protein subunit**
- **DNA**
- **RNA**
- **Inactivated virus**
- **Live-attenuated virus**
- **Replicating viral vectors**
- **Non-replicating viral vector**
- **Virus-like particle**

Vaccines undergoing Phase I Clinical Trials

- **RNA Vaccine**:
  - Uses mRNA-1273 , a novel lipid nanoparticle (LNP)-encapsulated mRNA that encodes for a full-length, prefusion stabilised spike (S) protein of SARS-CoV-2.

Vaccines undergoing Phase I Clinical Trials

- **Non-replicating Viral Vector Vaccine**
  - Uses an adenovirus type 5 vector for vaccine delivery. The same vaccine platform has been used as for the Ebola vaccine.

Major Global Stakeholders in Vaccine Development

Sinovac Biotech (China)COVID Vaccine

99% sure that their COVID-19 vaccine will work.

The company reached stage 2 of the coronavirus vaccine trial with more than 1000 volunteers participating. The company is in preliminary talks to hold stage 3 trials - the final part of the process in the UK.

Moderna (US) RNA vaccine

Phase I, non-randomised, open-label, dose ranging clinical trial is currently being conducted in 45 men and non-pregnant women, aged between 18 and 55 years at the National Institute of Allergy and Infectious Diseases (NIAID), Maryland, USA.

It set to move into the second phase of the clinical trials in July

Pfizer-BNTECH (US/UK)

CEO has claimed to make mRNA based vaccine available by October 2020

Details awaited

Oxford University (UK)Covid-19 vaccine

ChAdOx1 nCoV-19 is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) .

Investigators are assesing its effect in COVID-19 and it has already been administered to around 1000 subjects

In next phase, its planned to expand its administration in children also.

Novavax (US), NVX-CoV2373 Vaccine

A recombinant protein nanoparticle technology based vaccine. This technology is already being used against viruses that cause Hepatitis B and shingles.

The preliminary results of Phase-1 trial are expected in July 2020, after which Phase-II trials will begin in multiple countries.

Coronavirus Vaccine Progress in India

Serum Institute of India (SII) Vaccine : SII has partnered with the University of Oxford for the development of a safe and affordable coronavirus vaccine. Speeding up efforts to produce the vaccine doses as early as October 2020.

Zydus Cadila Vaccine: In Collaboration with Council of Scientific & Industrial Research (CSIR), Zydus is currently testing a "repurposed" vaccine against Covid-19 and has progressed to Phase-2 trial.Has sought approval from the drug controller for its wider use against the pandemic.

ICMR-Bharat Biotech Vaccine: Its been reported that ICMR-Bharat Biotech collaboration has signed an exclusive deal with the Thomas Jefferson University of Philadelphia to develop a new vaccine candidate for Covid-19. Novel vaccine was developed using an existing deactivated rabies vaccine as a vehicle for coronavirus proteins. Recently tested on animals, the vaccine showed a strong antibody response in mice.

PHARMACOVIGILANCE IN NTEP (National Tuberculosis Elimination Programme)

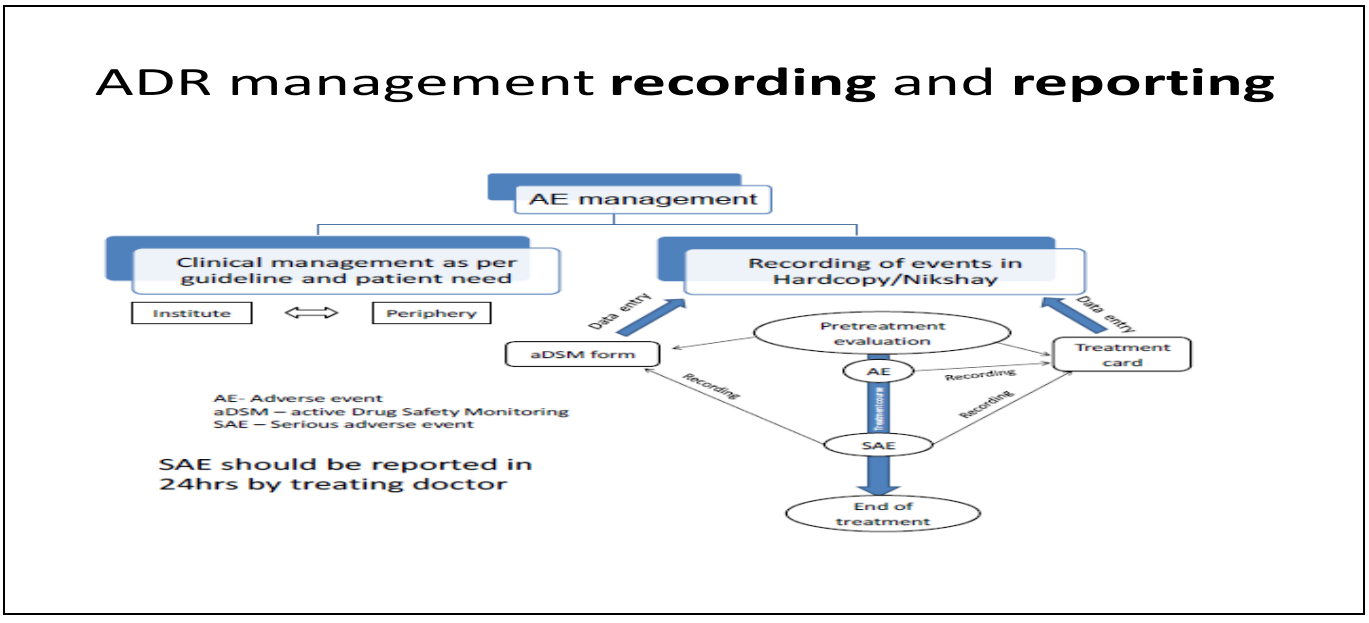
- To strengthen patient safety, safeguard patient's interest and ensure adherence to drug regimens, NTEP (Earlier RNTCP) formally entered into collaboration with the PvPI on October 11, 2013. NTEP in collaboration with PvPI and support from WHO India developed the comprehensive **active drug safety monitoring (aDSM) system** for active Pharmacovigilance of anti TB drugs. This aDSM defines the active and systematic clinical and laboratory assessment of patients on treatment to detect, manage and report suspected or confirmed drug toxicities. This aDSM system is expanded to all DR TB centres.

- The PvPI recommends reporting of any adverse event (AE) on the suspected ADR reporting form. This has been adopted by NTEP for drug susceptible TB patients put on first-line treatment. Based on a consensus between NTEP and PvPI, reporting of SAE is done using aDSM forms for all DR TB patients initiated on treatment in India.

- Active drug safety monitoring (aDSM) will follow the patient pathway from registration to the treatment outcome. The patient details are captured as baseline (before starting treatment) using the **aDSM — treatment initiation form** and will get updated for all SAEs using **aDSM — treatment review** form, after it is appropriately managed. Any Adverse Event (AE) will be captured additionally using NTEP PMDT treatment card. Both the aDSM — treatment initiation form and treatment review forms are filled in hard copy and also entered in NIKSHAY which is a web enabled and case-based monitoring application developed by National Informatics Centre (NIC). The data will be entered using the standard form in NIKSHAY. All SAEs and non-serious AEs must be reported to NTEP. All SAEs must be reported to AMC (ADR Monitoring Centre) and CTD (Central TB Division) using Nikshay within 24 hours. Once relevant aDSM forms are filled in Nikshay, information is directly communicated to PvPI through the electronic bridge that is functional.

- The ADR data submitted to Vigiflow will be analyzed by PvPI and shared with CTD on regular basis and the data with action required on immediate basis. The aDSM data will be analyzed at CTD. The relevant information will be shared with DSMC (Drug Safety Monitoring Committee) which evaluates it periodically, for patient safety and make recommendation to CTD regarding use of newer drugs.

- The overall objectives of aDSM are to reduce risks from drug-related harms in patients and to generate standardized aDSM data to design future policy updates on the use of such medicines.



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Drug Safety Alert (March-April 2020)

Sl No	Suspected Drug/Device	Indication	Adverse Drug Reaction/Safety Concern
1	EpiPen	Emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects and biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.[1]	1. Device failure from spontaneous activation caused by using sideways force to remove the blue safety release 2. Device failure from inadvertent or spontaneous activation due to a raised blue safety release 3. Difficulty removing the device from the carrier tube 4. User errors
2.	Montelukast	Bronchial Asthma and Allergy[2]	Suicidal thoughts or actions (Boxed Warning given)
3.	Hydroxychloroquine and Chloroquine	COVID-19[3]	Serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines

*https://www.fda.gov/drugs/drug-safety-and-availability/2020-drug-safety-communications Last accessed on 25/05/20

1. https://www.rxlist.com/epipen-drug.htm#indications Last accessed on 28/05/20
2. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug Last accessed on 27/05/20
3. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-o Last accessed on 25/05/20

New Drugs Approved (April 2020)

Sl No	Drug	Mechanism of action	Indication	Date of Approval
1	Opicapone	Peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor[1]	To treat patients with Parkinson's disease experiencing "off" episodes	24/4/2020
2	Sacituzumab govitecan	Antibody-drug conjugate (ADC) targeting TROP-2-expressing cancer cells to induce DNA-damage-mediated cell death.[2]	To treat adult patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease	22/4/2020
3	Pemigatinib	Orally bioavailable inhibitor of the fibroblast growth factor receptor (FGFR) types 1, 2, and 3 (FGFR1/2/3), which may result in the inhibition of FGFR1/2/3-related signal transduction pathways, with potential antineoplastic activity.[3]	To treat certain patients with cholangiocarcinoma, a rare form of cancer that forms in bile ducts	17/4/2020
4	Tucatinib	Orally bioavailable inhibitor of the human epidermal growth factor receptor tyrosine kinase ErbB-2 (also called HER2). Selectively binds to ErbB-2 and inhibits the phosphorylation of ErbB-2, which may prevent the activation of ErbB-2 signal transduction pathways, resulting in growth inhibition and death of ErbB-2-expressing tumor cells.[4]	To treat advanced unresectable or metastatic HER2-positive breast cancer	17/4/2020

* https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020 Last accessed on 20/05/20

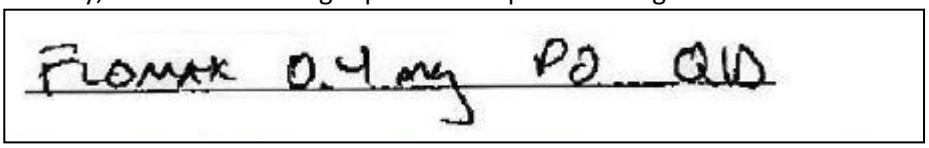
1. https://pubchem.ncbi.nlm.nih.gov/compound/Opicapone Last accessed on 21/05/20
2. https://www.drugbank.ca/drugs/DB12893 Last accessed on 25/05/20
3. https://pubchem.ncbi.nlm.nih.gov/compound/Pemigatinib#section=Pharmacology Last accessed on 21/05/20
4. https://pubchem.ncbi.nlm.nih.gov/compound/Tucatinib#section=Pharmacology-and-Biochemistry Last accessed on 29/05/2020

MEDICATION ERROR

Throughout healthcare facilities across world, "shortcuts" such as abbreviations and symbols are often used to save time when communicating medication orders, especially in handwritten communication. However, some of these shortcuts can be very time-consuming for the person on the receiving end to comprehend. Abbreviations and nonstandard dose designations are frequently misinterpreted, and they often lead to errors resulting in patient harm. As per the rational prescribing guidelines use of abbreviations should be avoided in the prescription because now it has been aptly proved by different studies that '**Abbreviations May Save Minutes; Prohibiting Abbreviations May Save Lives'.**

It has been commonly observed that, abbreviations used to indicate the frequency of drug administration (e.g., QD and QOD) can be problematic. With the aim to promote Safe Prescription Practices, one of the most common abbreviation errors from the prescription is shared herewith along with the list of abbreviations and its correct usage.

In one report received through the MERP, an order (see Figure) for Flomax (tamsulosin) 0.4 mg QD was misinterpreted as Flomax 0.4 mg QID. Fortunately, the error was caught prior to the patient being harmed.



List of Error Prone Abbreviations

Abbreviations	Intended Meaning	Misinterpretation	Correction
µg	Microgram	Mistaken as "mg"	Use "mcg"
AD, AS, AU	Right ear, left ear, each ear	Mistaken as OD, OS, OU (right eye, left eye, each eye)	Use "right ear," "left ear," or "each ear"
OD, OS, OU	Right eye, left eye, each eye	Mistaken as AD, AS, AU (right ear, left ear, each ear)	Use "right eye," "left eye," or "each eye"
BT	Bedtime	Mistaken as "BID" (twice daily)	Use "bedtime"
cc	Cubic centimeters	Mistaken as "u" (units)	Use "mL"
D/C	Discharge or discontinue	Premature discontinuation of medications if D/C (intended to mean "discharge") has been misinterpreted as "discontinued" when followed by a list of discharge medications	Use "discharge" and "discontinue"
IJ	Injection	Mistaken as "IV" or "intrajugular"	Use "injection"
IN	Intranasal	Mistaken as "IM" or "IV"	Use "intranasal" or "NAS"
HS	Half-strength	Mistaken as bedtime	Use "half-strength" or "bedtime"
hs	At bedtime, hours of sleep	Mistaken as half-strength	
IU**	International unit	Mistaken as IV (intravenous) or 10 (ten)	Use "units"
o.d. or OD	Once daily	Mistaken as "right eye" (OD-oculus dexter), leading to oral liquid medications administered in the eye	Use "daily"
OJ	Orange juice	Mistaken as OD or OS (right or left eye); drugs meant to be diluted in orange juice may be given in the eye	Use "orange juice"
Per os	By mouth, orally	The "os" can be mistaken as "left eye" (OS-oculus sinister)	Use "PO," "by mouth," or "orally"
q.d. or QD**	Every day	Mistaken as q.i.d., especially if the period after the "q" or the tail of the "q" is misunderstood as an "i"	Use "daily"
qhs	At bedtime	Mistaken as "qhr" or every hour	Use "at bedtime"
qn	Nightly	Mistaken as "qh" (every hour)	Use "nightly"
q.o.d. or QOD**	Every other day	Mistaken as "q.d." (daily) or "q.i.d. (four times daily) if the "o" is poorly written	Use "every other day"
q1d	Daily	Mistaken as q.i.d. (four times daily)	Use "daily"
q6PM, etc.	Every evening at 6 PM	Mistaken as every 6 hours	Use "6 PM nightly" or "6 PM daily"
SC, SQ, sub q	Subcutaneous	SC mistaken as SL (sublingual); SQ mistaken as "5 every;" the "q" in "sub q" has been mistaken as "every" (e.g., a heparin dose ordered "sub q 2 hours before surgery" misunderstood as every 2 hours before surgery)	Use "subcut" or "subcutaneously"
ss	Sliding scale (insulin) or ½ (apothecary)	Mistaken as "55"	Spell out "sliding scale;" use "one-half" or "½"
SSRI	Sliding scale regular insulin	Mistaken as selective-serotonin reuptake inhibitor	Spell out "sliding scale (insulin)"
SSI	Sliding scale insulin	Mistaken as Strong Solution of Iodine (Lugol's)	Spell out Strong Solution of Iodine
i/d	One daily	Mistaken as "tid"	Use "1 daily"
TIW or tiw	3 times a week	Mistaken as "3 times a day" or "twice in a week"	Use "3 times weekly"
U or u**	Unit	Mistaken as the number 0 or 4, causing a 10-fold overdose or greater (e.g., 4U seen as "40" or 4u seen as "44"); mistaken as "cc" so dose given in volume instead of units (e.g., 4u seen as 4cc)	Use "unit"

Adopted from * **ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations**