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Editorial

Risk benefit analysis is a key to in decision making for any therapeutic or prophylactic intervention. Unbiased and independent data analysis is the cornerstone for such analysis. Newer interventions need more critical analysis for the beneficial and harmful effects for making right decision, which will save both the unnecessary expenditure and reduce the chance of the harm by minimizing the use of risky intervention when risks outweigh the benefits. In this context, the drugs which have been in use for quite long time for other medical indications when found to be effective for newer indications are important as the safety data from widespread use is valuable which is not possible to get for new drugs or interventions. As with previous issues, this issue of the bulletin intends to focus on such issues and aims to provide independent and useful information for health care providers.

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Guideline for Treatment of Severe Malaria in Nepal

Severe falciparum malaria

Severe malaria is most commonly caused by infection with *Plasmodium falciparum,* although *P. vivax* and *P. knowlesi* can also cause severe disease. The risk is increased if treatment of an uncomplicated attack of

malaria caused by these parasites is delayed. Recognizing and promptly treating uncomplicated malaria is therefore of vital importance.

High parasitaemia is undoubtedly a risk factor for death from falciparum malaria, but the relation between parasitaemia and prognosis varies according to the level of malaria transmission. In low-transmission areas, mortality from acute falciparum malaria begins to increase with parasite densities over 100 000/µl (~2.5% parasitaemia), whereas in areas of higher transmission much higher parasite densities may be well tolerated.

Parasitaemia > 20% is associated with a high risk in any epidemiological context. A general overview of the features of severe malaria is given below.

The clinical manifestations can occur singly or, more commonly, in combination in the same patient.

Clinical features of severe malaria

- Impaired consciousness (including unarousable coma): A Glasgow Coma Score <11 in adults or a Blantyre Coma Score <3 in children.
- Prostration: Generalized weakness so that the patient is unable to sit, stand or walk without assistance
- Multiple convulsions: More than two episodes within 24h.
- Deep breathing and respiratory distress (acidotic breathing).

- Acute pulmonary oedema and acute respiratory distress syndrome:

Oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultations.

- Circulatory collapse or shock, systolic blood pressure < 80mm Hg in adults and < 50mm Hg in children
- Acute kidney injury/Renal Impairment.
- Clinical jaundice plus evidence of other vital organ dysfunction.
- Abnormal bleeding: Recurrent or prolonged bleeding from nose, gums or venepuncture sites; hematemesis or melaena.

Laboratory and other findings

- Hypoglycaemia (< 2.2mmol/l or < 40mg/dl)
- Metabolic acidosis (plasma bicarbonate < 15mmol/l)
- Severe normocytic anaemia (haemoglobin < 5g/dl, packed cell volume

  < 15% in children; <7g/dl, packed cell volume < 20% in adults)
- Haemoglobinuria
- Hyperlactataemia (lactate > 5mmol/l)
- Renal impairment: serum creatinine > 265µmol/l (3mg/dl) or Blood urea > 20mmol
- Pulmonary oedema (radiological).
- Hyperparasitaemia: P. falciparum parasitaemia > 10%

Therapeutic objectives

The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescent infection. Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.

Clinical evaluation of patient for severe malaria

In all patients ask about:

- Recent history of travel (to identify those coming from malaria free areas to areas of high transmission or those who have travelled to areas with heamorrhagic fever which may mimic malaria).
- Extreme weakness (Prostration) which is inability to eat and drink or do anything without support.
- Abnormal behaviour or altered consciousness.
- Convulsions: ask about the number of episodes, part of the body involved, previous history and time of onset of last episode.
- Time of last drink or food since the onset of the illness.
- Fast breathing which may occur due to pulmonary oedema or acidosis.
- Reduced urinary output (time patient last passed urine).
- Colour of urine: whether dark or coca-cola coloured (this may suggest excessive breakdown of red blood cells or dehydration).
- Pregnancy: in adult females.
- Ask history to exclude other severe diseases.

Physical examination

A detailed physical examination should be undertaken with the aim at assessing for the presence of signs of severe malaria, prognostics evaluation and identifying other possible causes of disease.

Laboratory confirmation and test

Every suspected case of severe malaria should have a parasitological diagnosis before treatment. Advantage can be taken of the availability of RDT to rapidly establish the diagnosis by the bedside. Blood smears can be sent to the laboratory for quantification of the parasite density and subsequent monitoring of patient's progress.

Other laboratory investigations are conducted with the aim to assess complications, exclude other possible causes of severe febrile illnesses and monitor the patients' progress.

Recommended tests to be routinely performed include:

- Haematocrit (PCV) and/or Haemoglobin concentration
- Blood sugar level
- Lumbar puncture in unconscious patients.
- Urinalysis
- Blood culture
- Feto-maternal surveillance in pregnant women

Other tests that could be required subject to the patients' specific situation and available facilities include:

- Blood electrolytes, urea and creatinine
- Chest X-ray
- Complete blood count
- Arterial Blood Gas (PO2, PCO2 and pH)

Treatment

Severe malaria is a medical emergency requiring in-patient care. Deaths from severe malaria can result either from direct effect of the disease or the complications. The provider should attend to the immediate threats to life first.

Specific antimalarial treatment

The antimalarial medicine recommended for the treatment of severe malaria is an initial treatment with injectable (IV/IM) artesunate followed by a full course of AL as soon as the patient is stable enough and able to tolerate oral medication.

Artesunate

Recommended Dosage for injectable artesunate:

– Children less than 20kg – artesunate 3.0 mg/kg bw

– Older children and adults – artesunate 2.4mg/kg bw

Dosage regimen - Give 3 parenteral doses of injection artesunate in the first 24 hours : first dose on admission (time zero), second dose 8 hours after the first dose and third dose at 24 hours after the first dose. Thereafter every 24 hours until patient is able to tolerate oral medication.

The parenteral antimalarial drugs should be given for a minimum of 24 h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up treatment with single dose of primaquine (PQ). Artesunate is to be reconstituted immediately before administration with bicarbonate and given either slowly intravenously or intramuscularly.

Severe *P. vivax* malaria

Although *P. vivax* malaria is considered to be benign, with a low case fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in P. falciparum malaria. Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria. Following parenteral artesunate, treatment can be completed with a full treatment course of oral artemether -lumefentrine and primaquine. A full course of radical treatment (14 days) with primaquine should be given.

Management of specific complications

Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown in Table 1.

Table 1: Immediate clinical management of severe manifestations and complications of P. falciparum malaria

Manifestation or complication	Immediate Management [a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is = 3 mmol/L for children <5 years and < 2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema[b]	Prop patient up at an angle of 45Â°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.

[a] It is assumed that appropriate antimalarial treatment will have been started in all cases.

[b] Prevent by avoiding excess hydration

Source: National Malaria Treatment Protocol 2019. Epidemiology and Disease Control Division Department of Health Services Teku, Kathmandu (July 2019).

Article Summary: Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs

The mRNA SARS-CoV-2 vaccines were released in response to the Covid-19 public health crisis. There is no precedent for using mRNA vaccines in the context of infectious disease. The numerous changes in the vaccine mRNA conceal the mRNA from cellular defenses, promoting a longer biological half-life and high spike protein production. The immune response to the vaccine, however, is very different from that of a SARS-CoV-2 infection.

Vaccination with an mRNA vaccine triggers a series of biological events that are not only distinct from those triggered by infection, but are also demonstrably detrimental to both short- and long-term immune competence and normal cellular function. These vaccinations have now been shown to downregulate critical cancer surveillance, infection control, and cellular homeostasis pathways. They introduce highly modified genetic material into the body.

In COVID-19 patients, but not in those received vaccine, differential gene expression analysis of peripheral dendritic cells revealed a dramatic upregulation of both type I and type II interferons (IFNs). One remarkable finding was that there was an increase in circulating hematopoietic stem and progenitor cells (HSPCs) in COVID-19 patients, but this increase was noticeably absent after vaccination. The vacconated people did not show the same striking increase in circulating plasmablasts as COVID-19 patients. All of these findings support the hypothesis that anti-COVID-19 vaccines actively suppress type I IFN signaling. Governments are hesitant to consider the possibility that these injections may cause harm in unexpected ways, and that such harm may even outweigh the benefits obtained in terms of disease protection. The antibodies induced by the vaccines now fade in as little as 3-10 weeks after the second dose, so people are advised to get booster shots at regular intervals. It has also become clear that rapidly emerging variants, such as the Delta and now the Omicron strain, are developing resistance to the vaccine-induced antibodies due to mutations in the spike protein.

The growing evidence that vaccines do little to control disease spread and that their effectiveness fades over time makes determining the extent to which vaccines may cause harm even more important. There is no doubt that SARS-CoV-2 modified spike protein mRNA vaccinations have biological effects. The implications are ominous because these vaccines are specifically designed to induce high and ongoing production of SARS-CoV-2 spike glycoproteins. As previously stated, inhibiting IRF9 inhibits TRAIL and all of its regulatory and downstream apoptosis-inducing effects. Exosomal microRNA suppression of IRF9 should also be expected to impair the cancer-protective effects of BRCA2 gene activity, which is dependent on that molecule as described above. Breast, fallopian tube, and ovarian cancer in women, prostate and breast cancer in men, acute myeloid leukemia in children, and other cancers are linked to BRCA2.

The goal of vaccination is to provide protection against the SARSCoV2 virus to everyone who receives it. This is accomplished by stimulating the immune system to produce antibodies against the virus as well as lymphocytes that retain memory and the ability to fight off the virus for an extended period of time. Adjuvants such as aluminum and squalene are commonly used in vaccines to stimulate immune cells to migrate to the injection site immediately after vaccination. In the early stages of mRNA vaccine development, it was hoped that the mRNA would act as its own adjuvant. This is because human cells recognize viral RNA as foreign, which causes an increase in type I IFNs via toll-like receptors such as TLR3, TLR7, and TLR8. However, it became clear that this approach had flaws, both because the intense reaction could cause flu-like symptoms and because IFN- could initiate a cascade response, leading to the breakdown of the mRNA before it could produce enough SARS-CoV-2 spike glycoprotein to induce an immune response (de Beuckelaer et al., 2016). A breakthrough occurred when it was discovered experimentally that the mRNA coding for the spike protein could be modified in specific ways to fool human cells into mistaking it for harmless human RNA.

Because of the short development time and the novelty of the technologies used, these vaccines will be deployed with several unresolved issues that only time will allow to resolve. Those vaccinated with SARS-CoV-2 BNT162b2 mRNA vaccines developed a robust adaptive immune response that was restricted only to memory cells, i.e., an alternative route of immune response that bypassed the IFN mediated pathways, in contrast to the immune response induced by natural SARS-CoV-2 infection, which is characterized by a robust interferon response. Furthermore, there is a significant loss of neutralizing antibodies induced by the BNT162b2 mRNA vaccine compared to those conferred by the SARS-CoV-2 mutants alone due to subsequent mutations in the SARS-CoV-2 spike protein. m6A mediates mRNA translation preferentially in a cap-independent manner under conditions of cellular stress, which can be induced by a viral infection or disease states such as cancer. This is in contrast to the effect of SARS-CoV-2 mRNA vaccination, which drives cells toward cap-dependent translation. Furthermore, under diverse cellular stress conditions, there is an overwhelming induction of transcriptome-wide addition of m6A, resulting in an increased number of mRNAs with 5′ UTRs enriched with m6A.

Exosomes are a component of the mRNA decay mechanism that work in tandem with stress granules (SGs) and P-bodies under stress conditions (PBs). There is an obvious resistance to promotion and assembly of the large decapping complex, and thus resistance to physiological mRNA decay processes, under conditions of vaccine-mRNA-induced translation, which could be called "excessive dependence on cap-dependent translation." This would imply that the fate of specific synthetic mRNAs is being omitted, which would otherwise be determined by the common cellular strategy for mRNA

turnover involving messenger ribonucleinproteins (mRNPs). Furthermore, when synthetic mRNAs are over-reliant on cap-dependent translation in SARS-CoV-2 vaccines, many native mRNAs with significant IRES and specific methylations (m6A) in their structure will prefer cap-independent translation, which is strongly linked to mRNA decay quality control mechanisms. Significant deadenylated mRNA products, as well as products derived from mRNA metabolism (decay), are thus directly linked to exosome cargoes.

The important distinction between the impact of vaccination versus natural infection on type I IFN is a central point of analysis. Natural infection promotes type I IFN production very early in the disease cycle, whereas vaccination actively suppresses it. Preexisting conditions frequently result in impaired type I IFN signaling, which leads to more severe, critical, and even fatal COVID-19. If the vaccine-induced impairment persists as antibody levels decline, it may result in a situation in which the vaccine causes a more severe disease expression than would have occurred in the absence of the vaccine. Another expected side effect of suppressing type I IFN is the reactivation of preexisting chronic viral infections. It has been demonstrated that mRNA vaccines primarily induce an immunoglobulin G (IgG) immune response, with less IgA and even less IgM production. The amount of IgG antibodies produced is comparable to that seen in severe COVID-19 cases. HIT is caused by IgG antibodies in complex with heparin. Exosomes produced by macrophages induced by the vaccine to synthesize SARS-CoV-2 spike glycoprotein increase the risk of thrombocytopenia in response to immune complexes formed by spike glycoprotein antigen and IgG antibodies produced against the spike glycoprotein.

Neurons in the brain have ACE2 receptors, which could be disrupted by S1 released from spike-glycoprotein-containing exosomes or spike-glycoprotein-producing cells that had taken up the vaccine nanoparticles. Within the paraventricular nucleus of the brain, Ang II increases TLR4-mediated signaling in microglia, activating them and increasing the production of reactive oxygen species, which causes tissue damage. Ang II synthesis increases when ACE2 receptor signaling is reduced. Elevated Ang II levels are a cause of neurodegeneration of the optic nerve, resulting in optic neuritis, which can result in severe irreversible visual loss. Human inner ear tissue expresses ACE2, furin, and the transmembrane protease serine 2 (TMPRSS2), all of which help viruses enter. They also demonstrated that SARS-CoV-2 can infect specific types of human inner ear cells. The ability of the SARS-CoV-2 virus to infect the ear was specifically investigated by looking at the expression of the receptor ACE2 as well as the enzymes furin and TM-PRSS2 in various types of cells in the middle and inner ears.

Considerations regarding the Vaccine Adverse Event Reporting System (VAERS)

Number of symptoms reported in VAERS, restricted to the US population, for the year 2021, for various adverse effects that could be caused by inflammation in associated syztems are shown in table with total counts for COVID-19 vaccines and for all vaccines. These events total over 200,000 in total, accounting for 97.2 percent of all entries related to any vaccine in 2021. This represents a significant 27.2 percent of all events associated with COVID-19 vaccines listed for 2021.

Table 1: Number of problems reported in VAERS, restricted to the US population, for the year 2021

Problems	Covid-19 Vaccines	All Vaccines
Deafness	2,895	3,033
Syncope	14,701	15,268
Vomiting	27,885	28,955
Myocarditis	2,322	2,361
Myocardial infarction	2,224	2,272
Thrombosis	3,899	3,951
Pulmonary embolism	3,100	3,137
Anosmia	3,657	3,677
Various Cancer	1,474	1,535

Conclusion

SARS-CoV-2 spike protein synthesis is promoted by mRNA vaccines. The spike protein is toxic to neurons and impairs DNA repair mechanisms. The suppression of type I interferon responses impairs innate immunity. mRNA vaccines may increase the risk of infectious diseases and cancer. Codon optimization produces G-rich mRNA with unpredictable and complex effects. Given the large number of people who received SARS-CoV-2 mRNA vaccines and the wide range of possible outcomes, billions of lives are potentially at risk.

Reference

Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs. Food and Chemical Toxicology. 2022 Jun 1;164:113008. https://doi.org/10.1016/j.fct.2022.113008.

Abstracts in Focus

Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review

Introduction: The common reported adverse effects of COVID-19 vaccination consist of the injection site's local reaction followed by several non-specific flu-like symptoms. However, rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) after viral vector vaccines (ChAdOx1 nCoV-19 vaccine, Ad26.COV2 vaccine) have been reported. Herein we systemically reviewed the reported cases of CVST and VITT following the COVID-19 vaccination.

Methods: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched PubMed until May 19, 2021, and the following Keywords were used: COVID Vaccine & Neurology, AstraZeneca COVID vaccine, ChAdOx1 nCoV-19 COVID vaccine, AZD1222 COVID vaccine, Janssen COVID vaccine, Johnson & Johnson COVID vaccine, Ad26.COV2 COVID vaccine. The authors evaluated the abstracts and titles of each article for screening and inclusion. English reports about post-vaccine CVST and VITT in humans were collected.

Results: Until May 19, we found 877 articles with the searched terms. We found 12 articles, which overall present clinical features of 36 patients with CVST and VITT after the ChAdOx1 nCoV-19 vaccine. Moreover, two articles were noted, which present 13 patients with CVST and VITT after Ad26.COV2 vaccine. The majority of the patients were females. Symptom onset occurred within one week after the first dose of vaccination (Range 4-19 days). Headache was the most common presenting symptom. Intracerebral hemorrhage (ICH) and/or Subarachnoid hemorrhage (SAH) were reported in 49% of the patients. The platelet count of the patients was between 5 and 127 cells×109/l, PF4 IgG Assay and d-Dimer were positive in the majority of the reported cases. Among 49 patients with CVST, at least 19 patients died (39%) due to complications of CVST and VITT.

Conclusion: Health care providers should be familiar with the clinical presentations, pathophysiology, diagnostic criteria, and management consideration of this rare but severe and potentially fatal complication of the COVID-19 vaccination. Early diagnosis and quick initiation of the treatment may help to provide patients with a more favorable neurological outcome.

Reference: Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci. 2021 Sep 15;428:117607. doi: 10.1016/j.jns.2021.117607. Epub 2021 Aug 3.

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel

Background: Approximately 5.1 million Israelis had been fully immunized against coronavirus disease 2019 (Covid-19) after receiving two doses of the BNT162b2 messenger RNA vaccine (Pfizer-BioNTech) by May 31, 2021. After early reports of myocarditis during adverse events monitoring, the Israeli Ministry of Health initiated active surveillance.

Methods: We retrospectively reviewed data obtained from December 20, 2020, to May 31, 2021, regarding all cases of myocarditis and categorized the information using the Brighton Collaboration definition. We analyzed the occurrence of myocarditis by computing the risk difference for the comparison of the incidence after the first and second vaccine doses (21 days apart); by calculating the standardized incidence ratio of the observed-to-expected incidence within 21 days after the first dose and 30 days after the second dose, independent of certainty of diagnosis; and by calculating the rate ratio 30 days after the second dose as compared with unvaccinated persons.

Results: Among 304 persons with symptoms of myocarditis, 21 had received an alternative diagnosis. Of the remaining 283 cases, 142 occurred after receipt of the BNT162b2 vaccine; of these cases, 136 diagnoses were definitive or probable. The clinical presentation was judged to be mild in 129 recipients (95%); one fulminant case was fatal. The overall risk difference between the first and second doses was 1.76 per 100,000 persons (95% confidence interval [CI], 1.33 to 2.19), with the largest difference among male recipients between the ages of 16 and 19 years (difference, 13.73 per 100,000 persons; 95% CI, 8.11 to 19.46). As compared with the expected incidence based on historical data, the standardized incidence ratio was 5.34 (95% CI, 4.48 to 6.40) and was highest after the second dose in male recipients between the ages of 16 and 19 years (13.60; 95% CI, 9.30 to 19.20). The rate ratio 30 days after the second vaccine dose in fully vaccinated recipients, as compared with unvaccinated persons, was 2.35 (95% CI, 1.10 to 5.02); the rate ratio was again highest in male recipients between the ages of 16 and 19 years (8.96; 95% CI, 4.50 to 17.83), with a ratio of 1 in 6637.

Conclusions: The incidence of myocarditis, although low, increased after the receipt of the BNT162b2 vaccine, particularly after the second dose among young male recipients. The clinical presentation of myocarditis after vaccination was usually mild.

Reference: Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021 Dec 2;385(23):2140-2149. doi: 10.1056/NEJMoa2109730. Epub 2021 Oct 6.

Role of Honey and *Nigella sativa* in the Management of Covid-19: HNS-COVID-PK trial

Purpose: Since, honey and Nigella sativa (HNS) have established antiviral, antibacterial, anti-inflammatory, antioxidant, and immunomodulatory properties, we tested their efficacy for this disease in a multicenter, placebo-controlled and randomized clinical trial at four medical care facilities in Pakistan.

Methods: RT-PCR confirmed COVID-19 adults showing moderate or severe disease were enrolled in the trial. Patients were randomly assigned in 1:1 ratio to receive either honey (1 g/Kg/day) plus Nigella sativa seeds (80 mg/Kg/day) or placebo up-to 13 days along with standard care.

Results: 210 with moderate and 103 with severe disease, underwent randomization from April 30 to July 29, 2020. Among the moderate cases, 107 were assigned to HNS whereas 103 were assigned to the placebo group. Among the severe cases, 50 were given HNS and 53 were given placebo. HNS resulted in 50% reduction in time taken to alleviate symptoms as compared to placebo (moderate cases: 4 versus 7 days, P<0.0001 and severe cases: 6 versus 13 days, P<0.0001). HNS also cleared the virus earlier than placebo in both moderate cases (6 versus 10 days, P<0.0001) and severe cases (8.5 versus 12 days, P<0.0001). In severe cases, mortality rate was less than 1/4th of that in HNS group than placebo (4% versus 18.87%, P=0.029). No HNS-related adverse effects were observed.

Conclusions: HNS, compared with placebo, significantly improved symptoms, expedited viral load clearance and reduced mortality in COVID-19 patients.

Clinical implications: The inexpensive over the counter treatment regimen would be a valuable source to lower the burden on healthcare system while significantly dampening impact of the disease.

Reference: Farooq I, Kalsoom L, Ashraf S . Role of honey and nigella sativa in the management of Covid-19: HNS COVID-PK trial. Chest. 2022 Jun;161(6):a150. doi: 10.1016/j.chest.2021.12.182. epub 2022 Jun 20

Chronic Effects of Nicotine in Adolescent Brain and Behavior and Pharmacological Approach to Smoking Cessation

Adolescence is a time of major plasticity of brain systems that regulate motivated behavior and cognition, and is also the age of peak onset of nicotine use. Although there has been a decline in teen use of cigarettes (in western countries) in recent years, there has been a huge increase in nicotine vaping. It is therefore critically important to understand the impact of nicotine on this critical phase of brain development. Animal studies have also shown that nicotine has unique effects on adolescent brain.[1] Some of the chronic effects of nicotine in adolescents are:

Withdrawal syndrome

Abrupt cessation of tobacco use in dependent smokers results in withdrawal symptoms that include both somatic and affective components. Somatic symptoms include bradycardia, insomnia, and gastrointestinal discomfort, whereas negative affective symptoms include anger, anxiety, craving, depression, difficulty concentrating, impatience, insomnia, and restlessness. There is limited research on withdrawal from e-cigarettes, but recent analysis of the US Population Assessment of Tobacco and Health Survey and a clinical trial by the same investigators indicated that withdrawal symptoms were mild in never smokers, whereas another study of self-reported dependence symptoms suggested there were similarities to tobacco dependence but with some unique indicators. A recent study has reported that teen e-cigarette users are more likely to report dependence signs and be daily users if they use high nicotine content pods.

Nicotine withdrawal following chronic passive administration in animals results in a syndrome with both somatic and affective components, including disrupted operant performance, avoidance behavior, weight gain, anxiety-like behaviors, decreased reward sensitivity, and opioid-like withdrawal behaviors. Although these withdrawal signs are routinely seen in adult rodents, this is not the case for adolescents. In most studies, male adolescents have been found to exhibit less prominent somatic withdrawal symptoms than adults, although female adolescent mice have been reported to show increased physical withdrawal signs as compared to adults. There is a notable discrepancy between human studies, in which teens are thought to be more sensitive to withdrawal than adults, and preclinical studies where the opposite is observed. One possible reason is that route and timing of nicotine administration may make a difference, as has been shown in one prior rodent study.[2] Alternatively, tobacco constituents, which have been shown to enhance reinstatement of nicotine seeking behavior, may increase withdrawal signs. Further studies are needed to address this issue.

Drug reward

Many studies have shown long-term consequences of adolescent nicotine exposure on drug reward. Adolescent nicotine treatment increases subsequent nicotine reward and decreases aversion in adults. This may reflect an age-dependent increase in α5, α6 and β2 nAChR subunits in the ventral midbrain. These findings are also consistent with clinical data, which show that teen e-cigarette use is associated with greater risk for subsequent initiation and continuation of cigarette smoking.

Adolescent nicotine also leads to increased rewarding effects of other abused drugs. Human studies indicate that smoking and e-cigarette use is associated with greater alcohol consumption in adolescents. Adult dependent smokers are also much more likely to be alcoholics than non-smokers, and the great majority of alcoholics smoke. Furthermore, there is a strong relationship between early onset of smoking and alcohol dependence and problem use. Since most smokers begin before the age of 18, it is critical that animal studies model the impact of adolescent nicotine exposure on alcohol intake and evaluate underlying mechanisms.

Preclinical studies have confirmed a positive interaction of nicotine with psychostimulants, particularly following adolescent nicotine exposure. Animals treated with nicotine during early adolescence, but not late adolescence or adulthood, have been found to have enhanced rewarding effects of cocaine, methamphetamine and morphine, as measured by conditioned place preference later in adulthood.

Cognition

The hippocampus is a brain region that is critical for memory formation and retrieval, and plays an important role in processing contextual information and spatial learning. Contextual fear learning is a hippocampal-dependent task in which performance is impacted by adolescent nicotine treatment. Animals treated with nicotine as adolescents that were tested as adults showed decreased context-induced freezing, and were less sensitive than saline-treated controls to nicotine enhancement of performance, effects that were not seen in adults treated with nicotine. Similar performance decrements were observed in another contextual conditioning task following adolescent nicotine treatment.

A tobacco-induced neurotoxicity of adolescent cognitive development (TINACD) theory has been proposed which postulates that smoking during early adolescence, a period of major neurodevelopment of brain structures regulating inhibitory control, leads to increased impulsivity and inattention.[3] In particular, the prefrontal cortex, which plays a critical role in integrating emotional and motivational states to regulate top-down attentional processes, is still actively maturing during adolescence and is a target for aberrant nicotine effects.

Emotional regulation

There is a strong association between teen use of tobacco products and anxiety and depression. Whereas many studies suggest that tobacco use is preceded by emotional dysregulation, and may be a form of self-medication, there is substantial evidence for a bidirectional association between smoking/vaping and depression. Other predictors of teen and young adult smoking include anhedonia, aggression, low hedonic capacity and lower distress tolerance.

Many animal studies have also shown a correlation between chronic adolescent nicotine exposure and long term increases in anxiety and depression. Nicotine treatment during adolescence, but not adulthood, increases anxiety in later life, as shown by elevated plus maze, time spent in the light side of a box, or time spent in the center zone of an open field. Several studies have also shown an age-specific increase in long-term depressive symptoms and anhedonia, as measured by immobility in the forced swim test and decreased sucrose preference. Thus, adolescent nicotine exposure may produce a long-term vulnerability to the adverse effects of stress, resulting in a negative emotional state. Mechanistic analyses have shown that adolescent nicotine induces profound and long-lasting neuronal and molecular alterations in regions that are critical for emotional regulation. In particular, the behavioral alterations are accompanied by increased firing frequency and bursting of neurons in the VTA and prefrontal cortex. A selective downregulation of dopamine D1 receptor expression in the prefrontal cortex has also been observed, which may have may have occurred in response to elevated sub-cortical dopaminergic firing and bursting. Clinical studies have previously shown that striatal levels of the D1 receptor are negatively associated with major depression, particularly in those with anger attacks.

Pharmacological approach to smoking cessation

Different pharmacological strategies are available to treat smoking dependence. They should be associated with non-pharmacological strategies (behavioral counselling), which are validated approaches to promote the process of quitting. The main pharmacological treatments available for smoking cessation are the following: nicotine replacement therapy (NRT), varenicline, bupropion and cytisine.[4]

The clinician should follow both currently available scientific evidence and patient's preference for a proper choice of one therapy over another, paying particular attention to those patients having contraindications to these drugs due to the presence of specific comorbidities (i.e. Cardiovascular, renal, hepatic, psychiatric comorbidities).

Nicotine replacement therapy (NRT)

Nicotine replacement therapy is based on the controlled administration of nicotine, making it easier to abstain from tobacco by partially replacing the nicotine previously obtained from tobacco use. Nicotine replacement therapy aims both to stimulate nicotine receptors thus removing smoking craving and withdrawal symptoms (this effect is immediate), and to reduce the number of nicotine receptors (this effect is slower and continues for weeks progressively reducing tobacco dependence).

Controlled administration of nicotine reduces the positive effects induced by smoking thanks to a lower dosage and slower pharmacokinetics. Nicotine is more slowly absorbed generating lower but prolonged blood peaks, compared to cigarettes, thus reducing rewarding effects and withdrawal symptoms including irritability, anxiety, difficulty concentrating, dysphoria, increased appetite, weight gain, and sleep disorders. Each different NRT product has demonstrated the same efficacy in achieving smoking cessation. Consequently, the choice of the NRT product should reflect the patient's preferences. However, a combination of transdermal nicotine patch with a more rapidly absorbed NRT (i.e. oro-nasal products) is more effective than the use of a single product.

Nicotine replacement therapy usually lasts 12 weeks, although treating heavy smokers for longer intervals may be reasonable, at least until the patient feels confident enough not to relapse. Long-term NRT is not associated with increased incidence of harm. Longer therapeutic intervals are particularly indicated in patients with psychiatric or other substance use disorders.

Varenicline

Varenicline is a partial agonist selective for α4β2 nicotinic acetylcholine receptors (nAChRs), one of the receptors related to dopamine release following nicotine binding. Varenicline activates the α4β2 receptor with a maximal effect about 50% that of nicotine, alleviating symptoms of craving and withdrawal (agonist activity), while simultaneously reducing the rewarding by preventing nicotine binding (antagonist activity). Ultimately, varenicline promotes smoking cessation

by preventing withdrawal symptoms while moderate levels of dopamine are maintained in the brain.

Smokers should stop smoking one to two weeks after the first dose of varenicline, in order to reach the steady state. The pre-medication phase may be prolonged to 4 weeks to increase efficacy. The drug is progressively titrated to minimize side effects, mainly gastrointestinal symptoms such as nausea. An additional course of 12 weeks treatment with varenicline at 1 mg twice daily may be considered for the maintenance of abstinence in patients who have successfully stopped smoking at the end of the therapeutic interval (12 weeks).

Bupropion, sustained release (SR)

The precise mechanism of action of bupropion is not well understood. Bupropion is likely to exert its pharmacological effects by weakly inhibiting the reuptake of both dopamine and norepinephrine, therefore prolonging their duration of action within the neuronal synapse and their downstream effects. When taken to quit smoking, bupropion may confer both anti-craving and anti-withdrawal effects by inhibiting dopamine reuptake, which mediates the reward pathways associated to nicotine use, and through the antagonism of the nicotinic acetylcholinergic receptor. Bupropion also acts by alleviating some of the symptoms of nicotine withdrawal, which include depression, reducing the overall severity of withdrawal syndrome. Highly nicotine-dependent smokers who receive bupropion are more likely to experience a decrease in depressive symptoms associated with abstinence.

Bupropion should be started before the patient's planned quit day. The patient should set a "target quit date" within the first 2 weeks of therapy and could continue smoking during treatment since this does not significantly affect the pharmacodynamics of bupropion. Steady-state blood levels are usually achieved after 1–2 weeks of treatment. If the patient is not able to quit within the target date, it is possible to delay smoking suspension until the third or fourth week of treatment or when abstinence is reached. The recommended and maximum dosage of bupropion is 300 mg daily (150 mg twice daily). The dosage could be decreased to 150 mg daily if the patient does not tolerate the entire dose due to adverse reactions occurrence.

Cytisine

Cytisine is a natural alkaloid found in several plant genera, such as Cytisus Laburnum and Sophora Tetraptera. Cytisine acts similarly to varenicline. It is a partial agonist selective for α4β2 nicotinic acetylcholine receptors, responsible for nicotine effects, and it prevents nicotine binding, thus reducing rewarding and both withdrawal symptoms and craving. Cytisine is available as oral tablets containing 1.5 mg of active principle. Clinical data on cytisine found an efficacy similar, or even higher, than NRT regarding the likelihood of smoking cessation. However, cytisine has a greater propensity to adverse events, even though they are mainly minor such as nausea, vomiting, and sleep disorders.

The recommended dose is 1 tablet (1.5 mg) every 2 h up to 6 tablets per day on day 1–3. In the meantime, the patient should reduce smoking to avoid nicotine overdosing symptoms. If the desired therapeutic effect is not obtained, the treatment should be interrupted and another cycle could be attempted after 2–3 months.

Combination therapy

If we consider pharmacodynamics, it is possible to speculate that combination therapy with different drugs having complementary modes of action should achieve better outcomes. Indeed, the FDA approved both the combination NRT and the combination of single NRT and bupropion for smoking cessation.

The Italian Society of Tobaccology (Società Italiana di Tabaccologia—SITAB) guidelines suggest the following combination therapies: long-term use of nicotine patches (more than 14 weeks) plus a short-term NRT product (gum or spray) or nicotine patches plus bupropion SR. There is no evidence of contraindications for the use of NRT plus varenicline, but results on efficacy are not univocal. Further research is needed to support the efficacy of this approach in clinical practice. All treatments including NRT, varenicline and bupropion are effective for smoking cessation. Their efficacy and safety have been validated even in patients with chronic CV disease. Combination therapies are justified for patients with a major nicotine addiction or who have used monotherapies which have failed because of relapses.

Conclusion

Smoking is associated with decreased quality of life and increased morbidity as well as mortality. Smoking cessation strategies are to be implemented in every clinical context, particularly in those involved in CV risk management and prevention. The pharmacological approach to smoking cessation is generally safe and effective, and therefore should be offered to everyone willing to quit smoking. It is never too late to quit smoking, and we should be able to reduce the morbidity and mortality related to smoking significantly by wide availability of de-addiction services.

References

1. Leslie FM. Unique, long term effects of nicotine on adolescent brain. Pharmacol Biochem Behav 2020; 190:173010. doi:10.1016/j.pbb.2020.173010.
2. Kota D, Martin BR, Damaj MI. Age-dependent differences in nicotine reward and withdrawal in female mice. Psychopharmacology 2008;198(2):201-10. doi: 10.1007/s00213-008-1117-8.
3. de Bry SC, Tiffany ST. Tobacco-induced neurotoxicity of adolescent cognitive development (TINACID): a proposed model for the development of impulsivity in nicotine dependence. Nicotine Tob Res 2008;10(1):11-25. doi: 10.1080/14622200701767811.
4. Giulietti F, Filipponi A, Rosettani G, Giordano P, Iacoacci C, Spannela F, Sarzani R. Pharmacological approach to smoking cessation: an updated review for daily clinical practice. High Blood Press Cardiovasc Prev 2020;27(5):349-62. doi: 10.1007/s40292-020-00396-9.

Drug Repurposing

Introduction

Drug repurposing is a novel way of finding new uses outside the scope of the original medical indication for existing drugs. Other terms which are widely used in this context are drug repositioning, drug reprofiling or drug re-tasking.[1] Drug repurposing offers a number of advantages over conventional drug discovery and development as outlined: a) Faster development timeline: Far shorter time periods for drug development compared to the conventional method because of the availability of preclinical, safety and tolerability data. b) Reduced cost: Since much of the preclinical and phase I/II work is already done, repurposing of a drug for a new indication will accrue significant savings. c) Faster regulatory approval: Since a repurposed drug already has a positive preclinical and safety data, regulatory approval will be easier and faster to obtain.[1,2] d) Higher odds of success: A reduced development cost and faster approval in turn may translate into a better and faster return on investment once the repurposed drug is marketed. e) Further understanding of disease mechanisms: A repurposed drug may reveal new targets, pathways and biomarkers hitherto unknown in a disease. This will enable further research into disease mechanisms and may lead to development of newer molecules structurally similar but more potent to the repurposed drug.[1]

Rationale for drug repurposing

Many lead compounds showing efficacy in the pre-clinical phase fail in subsequent clinical trials. Escalating developmental costs, high failure rates and an ever-increasing time to get the molecule from bench to approval has transformed the pharma industry into a less attractive investment. Drug repurposing is widely considered as a way out of this 'crisis'; repurposing of a drug which already possesses a favourable safety profile into the market for a different indication not only saves time but also enhances potential returns on investment.[1] Two of the biggest examples historic opportunities in drug repurposing are thalidomide and sildenafil citrate.[1,2]

Thalidomide

The journey of thalidomide from being a 'prescription for disaster' to a place on the WHO 'List of Essential Medicines' is an excellent example of the resurrection of an infamous teratogen through repurposing. The drug was very popular as an anti-emetic in pregnant woman suffering with morning sickness; it was also cheap and sold over the counter. In 1961, Dr William McBride, an Australian obstetrician, and Dr Widukind Lenz, a German paediatrician, made independent observations linking thalidomide use in pregnancy to congenital malformations. These findings were confirmed by multiple cases worldwide, and the drug was ultimately withdrawn from the market. Thalidomide was reported to cause limb and bone abnormalities such as amelia, phocomelia, syndactyly and underdeveloped long bones among other deformities.[1]

The first instance of repurposing thalidomide arose following the report by Dr Jacob Sheskin from the Hadassah University Hospital and Hansen Leper Hospital in Jerusalem in 1964. Sheskin observed an unexpected and dramatic resolution of the lepra skin eruption within 48 hours of administration in a patient with erythema nodosum leprosum (ENL) where thalidomide was used as a sedative. It acts by inhibition of tumour necrosis factor-α (TNF-α) involved in the pathogenesis of nerve damage in leprosy and other mechanisms contributing to its anti-inflammatory effect.[1,2]

In 1994, D'Amato and colleagues postulated that thalidomide-induced birth defects were due to the drug's inhibition of vasculogenesis in developing fetal limb bud and suggested that the same mechanism could be exploited for inhibition of tumour angiogenesis. Increased bone marrow microvascular density and elevated concentration of vascular endothelial growth factor in the serum suggested an important role for angiogenesis in the pathogenesis of myeloma and there came a potential opportunity to test thalidomide for a second indication. One of the first clinical trials conducted by investigators at the University of Arkansas in 1999 reported a 32% overall response rate with single-agent thalidomide in a series of 84 refractory plasma cell myeloma patients; this was confirmed by further studies. Thalidomide in combination with dexamethasone was officially approved by the FDA in 2006 for the treatment of multiple myeloma.[1,2]

Sildenafil

In the mid-80s, Pfizer was investigating selective inhibition of phosphodiesterases (PDE), a family of enzymes in the vascular smooth muscle, as a desire to develop alternate therapeutic strategies to nitrates due to their inherent adverse effects. Modulating downstream of the nitric oxide (NO)/cGMP pathway by inhibition of PDE5 was one such strategy that led to the development of novel pyrazolopyrimidines, later called sildenafil citrate.[1]

Sildenafil showed very good potency against PDE5 and excellent selectivity over other PDEs; it also showed vasodilatory effects, abrogated platelet aggregation, and inhibited thrombus reformation in a damaged carotid artery. In clinical studies with doses of up to 75 mg three times per day for 10 consecutive days, several volunteers reported penile erections as a side effect. Penile erections observed with sildenafil, together with emerging data implicating NO as a key mediator of the neural and haemodynamic effects that lead to penile erection in men, led Pfizer to undertake pilot studies of the drug in Erectile Dysfunction. NO is the neurotransmitter that is released from cavernous nerves during sexual stimulation. It diffuses into the vascular smooth muscle cells of the penis, stimulating the production of cGMP and leading to corpus cavernosum smooth muscle relaxation, vasocongestion, constriction of the venous outflow from the penis, and, ultimately, erection. The Pfizer researchers postulated that the administration of an inhibitor of cGMP breakdown would enhance and prolong the vasodilatory response, but only during sexual stimulation.[1,2]

Completion of separate clinical studies confirmed that single

doses of sildenafil can enhance erectile responses to sexual stimulation and be well tolerated; moreover, a clear dose–response relationship was observed. Efficacy response rates of 70% or higher were consistently observed in clinical trials. The FDA and EU approved sildenafil for the treatment of men with ED in 1998. Sildenafil has also been repurposed to other indications, the prominent one being the treatment of pulmonary arterial hypertension (PAH).[1, 2]

Ivermectin

This well-established anti-parasitic agent has been found to be effective in treatment of COVID-19. The details are available in the Vol.1 Issue 3 of this bulletin.

Methods and technologies for drug repurposing

A systematic approach built on the utilization of 'big data', harnessing the power of computing and the use of high-throughput screening methodologies (termed as 'systematic repurposing') has become the way forward in drug repurposing. Examples include the potential repurposing of topiramate, an anti-epileptic drug in inflammatory bowel disease, denosumab in Crohn's disease; and fasudil, an autophagy enhancer identified by the *drug-drug similarity approach* for potential use in amyotrophic lateral sclerosis (ALS).[1]

Access to a large selection of preclinical and clinically used/withdrawn compounds is another major requirement for repurposing and an area where various challenges exist. There is a role for academia, industry and clinicians in drug repurposing, but there are also newer players emerging such as venture capitalists and patient advocacy groups.[1]

Challenges in drug repurposing

The main challenges faced by repositioners lie in the relatively weak intellectual property protection afforded to such medicinal products, which can reduce their return on investment and discourage companies from developing them.[2] Another one of the major issues associated is about incentivizing repurposing. Patenting a new 'repurposed' indication is another hurdle; this can have a huge impact on the potential returns from the repurposed product and without some form of patent protection, investment in the development is rarely justified.[1,2] Regulatory approvals as well as exclusivity periods extended in different markets vary but they are important determinants of the success of a repurposed product.[1]

Conclusion

As for the future of drug repurposing, changes in pricing and patients' desire for therapeutic solutions irrespective of the rarity of disease will be the driving factors for this approach in the future. Factors such as advancement in technology, improvement in computing power and Artificial Intelligence, newer methods to utilize 'big data', changing perceptions on the part of various stakeholders in drug development and most importantly emerging diseases like COVID-19 and our need for effective drugs will drive the development of this innovative approach.[1]

References:

1. Pushpakom S. Chapter 1: Introduction and Historical Overview of Drug Repurposing Opportunities. In: Drug Repurposing. 2022. p. 1-13. DOI: 10.1039/9781839163401-00001
2. Jourdan J-P , Bureaua R, Rochaisa C and Dallemagnea P. Drug repositioning: a brief overview. *Journal of Pharmacy and Pharmacology*.2020;72:1145–1151. doi:10.1111/jphp.13273

Patient-related services provided by Department of Pharmacology, College of Medicine, NAIHS

1. Drug information services at College of Medicine.
Drug and therapeutics-related questions are answered from the department.
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KEY MESSAGES OF THE ISSUE

1. *Severe malaria is most commonly caused by infection with Plasmodium falciparum, although P. vivax* and *P. knowlesi* can also cause severe disease. The risk is increased if treatment of an uncomplicated attack of malaria caused by these parasites is delayed. Management of severe malaria requires clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care. The antimalarial medicine recommended for the treatment of severe malaria is an initial treatment with injectable (IV/IM) artesunate followed by a full course of artemether and lumefantrine as soon as the patient is stable enough and able to tolerate oral medication. Complications are to be managed in addition to the specific treatment of malaria.
2. SARS-CoV-2 spike protein synthesis is promoted by mRNA vaccines. The spike protein is toxic to neurons and impairs DNA repair mechanisms. The suppression of type I interferon responses impairs innate immunity. mRNA vaccines may increase the risk of infectious diseases and cancer. Codon optimization produces G-rich mRNA with unpredictable and complex effects.

3. Vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) are severe and potentially fatal complication of the adenovirus vector COVID-19 vaccination. The platelet count of the patients was between 5 and 127 cells$\times 10^9$/l, PF4 IgG Assay and d-Dimer were positive in the majority of the reported cases. Early diagnosis and quick initiation of the treatment may help to provide patients with a more favorable neurological outcome.
4. The incidence of myocarditis increased after the receipt of the BNT162b2 COVID-19 vaccine, particularly after the second dose among young male recipients has been significant. The overall risk difference between the first and second doses was 1.76 per 100,000 persons (95% confidence interval [CI], 1.33 to 2.19), with the largest difference among male recipients between the ages of 16 and 19 years (difference, 13.73 per 100,000 persons; 95% CI, 8.11 to 19.46). As compared with the expected incidence based on historical data, the standardized incidence ratio was 5.34 (95% CI, 4.48 to 6.40) and was highest after the second dose in male recipients between the ages of 16 and 19 years. The clinical presentation of myocarditis after vaccination has been usually mild but long-term studies are needed for further conclusion on long-term effects.
5. Honey (1 g/Kg/day) plus *Nigella sativa* seeds (80 mg/Kg/day) compared with placebo up-to 13 days along with standard care showed significantly improved symptoms, expedited viral load clearance and significantly reduced mortality in COVID-19 patients in a multicenter, placebo-controlled randomized clinical trial at four medical care facilities in Pakistan. The inexpensive and widely available treatment regimen would be a valuable source to lower the burden on healthcare system while significantly dampening impact of the disease.
6. Adolescent nicotine exposure may produce a long-term vulnerability to the adverse effects of stress, resulting in a negative emotional state. Mechanistic analyses have shown that adolescent nicotine induces profound and long-lasting neuronal and molecular alterations in regions that are critical for emotional regulation. Smoking cessation strategies should be implemented in every clinical context, particularly in those involved in CV risk management and prevention. The pharmacological approach to smoking cessation is generally safe and effective, and therefore should be offered to everyone willing to quit smoking.
7. Drug repurposing is the use of a drug in an indication other than the one for which it was initially marketed. Its origins lie mainly in the attrition experienced in recent years in the field of new drug discovery. A more rational approach to the identification of drug candidates for repositioning is possible, especially using data mining.

Please send your comments, suggestions and contributions for upcoming issues on the following address:

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