News from here and there

Fixed-dose combinations for treatment of diabetes unsafe, finds study

In a first-of-its-kind study published in the March 2018 issue of the *British Medical Journal Global Health*, researchers from the University of Edinburgh and Newcastle University, UK, and University of Massachusetts, Amherst, USA, have analysed and exposed grave insufficiencies in the evidence base for fixed-dose combinations (FDCs) containing metformin for type 2 diabetes (T2D) and have questioned the role of multinational companies (MNCs) in the manufacture and sale of these drugs to the Indian populace.

With over 60 million Indians suffering from T2D, one of the sobriquets used to describe our country is 'The diabetes capital of the world'. There is increasing concern both at the national and international levels about the drug regulatory system in India. The drug market in India has a large number of unapproved medicines and invalid combinations of both approved and unapproved drugs for T2D.

Despite the fact that national and international guidelines do not recommend FDCs for the treatment of T2D (because constant monitoring and dosage adjustment is needed to maintain adequate blood glucose levels), more than two-thirds of all medicines for diabetes sold in India are metformin FDCs. Ironically, some of these drugs are not approved by the national regulatory body, the Central Drugs Standard Control Organization (CDSCO), whose role is similar to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

CDSCO has approved 52 FDCs for T2D, resulting in more than 500 brands of metformin FDCs. With only two metformin FDCs approved in the USA, one in Australia, and none in the UK or Canada, the dissimilarities are obvious.

Five of the top-selling FDCs are manufactured by MNCs. In March 2016, the Government of India while banning 344 irrational FDCs, banned different dosages of three of the five top-selling metformin FDCs. The Delhi High Court lifted the ban in December 2016, and the same was upheld by the Supreme Court of India in December 2017, which required the Drugs Technical Advisory Board to consider the banned drugs and submit a report within 6 months.

The study reviewed both published and unpublished clinical trials for the top five selling metformin FDCs and compared them with four WHO criteria from clinical trial guidelines for the approval of FDCs. Only one study evaluated the effectiveness and safety of the combination versus the simultaneous use of the individual drugs as single-drug formulations. This clinical trial was found to be underpowered and of poor quality.

The study recommends the following policy changes:

1. CDSCO must publish the safety and efficacy data it considered when approving the metformin FDCs. If the results are on the basis of trials that are not of WHO standards, the FDCs must be banned immediately.
2. There must be transparency of clinical trial data, and the databases must be continually updated with protocols and outcomes.
3. There is need for an urgent review of the FDCs, based on WHO recommendations so that irrational FDCs do not enter the Indian pharmaceutical market.

The issues mentioned are not confined to our country alone. India is also known as 'The pharmacy of the developing world'. This means that these drugs will find their way to other parts of the globe sooner or later. Thus, it is now a concern for patients, healthcare professionals and authorities across the world.

It is worth noting that activists in India have long been campaigning against irrational FDCs, and the first case was filed in the Supreme Court of India way back in 1994.

Dr Anurag Bhargava (Professor, Department of Medicine, Yenepoya Medical College, Mangalore, and Adjunct Professor, Department of Medicine, McGill University, Canada), told this correspondent: 'In the West only a limited number of antidiabetic FDCs (limited to combinations of two antidiabetics) have been approved, which are supported by trial data. According to most guidelines, metformin is the initial drug of choice for most diabetics, and should be used in an optimal dose before adding another drug. However, in India, most patients are initiated on an antidiabetic FDC, mainly combinations of metformin and sulphonylurea. I have seen patients who either have persistent uncontrolled diabetes related to the suboptimal dose of metformin in these FDCs or develop hypoglycaemia as a result of the sulphonylurea. There are combinations of three, and even four, antidiabetic drugs with varying strengths that make any titration of doses impossible. FDCs, as they now exist, create confusion rather than convenience, and seriously increase the risk of prescription and dispensing errors. In the absence of adequate trial data, the safety and efficacy of antidiabetics in India is questionable, and all such FDCs (both approved and unapproved) should be subjected to rigorous scrutiny and immediate regulatory action. While India's pharmaceutical industry has earned a justified reputation for the manufacture of good quality and low-cost single-ingredient medicines and rational FDCs, the state of regulatory anarchy and apathy pointed out by this article recently, and by drug activists for more than two decades, reflects extremely poorly on India's regulatory authorities, its manufacturers, and its prescribers.'

P.M. NISCHAL, *Bengaluru, Karnataka*

Unicef raises issue of stagnation in control of malaria

On 25 April 2018, Unicef issued a press release highlighting some lesser-known facts about malaria. These included identification of the most susceptible portions of the population, including children under 5 years of age (for whom malaria is the third highest killer among communicable diseases, after pneumonia and diarrhoea), people from the poorest and most marginalized socioeconomic sections of society and pregnant women and their unborn children. The report also recognized countries that bear the maximum impact of malaria globally, such as Nigeria, the Democratic Republic of the Congo, India, Mozambique, Ghana, Angola, Uganda, Mali, Burkina Faso,

Kenya, Tanzania, Cameroon, Niger, Guinea and Chad. Four of five malaria-related deaths occur in these countries. The press release also suggested effectiveness of simple malaria-prevention measures such as sleeping under an insecticide-treated bed net. In 2016, an estimated 54% of people at risk of malaria in sub-Saharan Africa slept under an insecticide treated net compared to 30% in 2010. Countries that have achieved at least 3 consecutive years with no local cases of malaria have been certified as having eliminated malaria. In the past decade, these include United Arab Emirates (2007), Morocco (2010), Turkmenistan (2010), Armenia (2011), Maldives (2015), Sri Lanka (2016) and Kyrgyzstan (2016).

The report also highlighted worrying statistics of a slowdown in the progress on malaria control. In 2016, a total of 91 countries reported 216 million cases of malaria—5 million more than in 2015. This amounts to almost half the world's population—about 3.2 billion people—being at risk of malaria. Rwanda and Nigeria together saw an increase of over 1.5 million cases, while the Democratic Republic of Congo recorded an additional 500 000 cases in 2015–16. Nearly 300 000 children under 5 years of age died of malaria in 2016—equivalent to nearly 800 young lives lost each day. An estimated 90% of malaria deaths occurred in sub-Saharan Africa, with 407 000 deaths in 2016. The rate of increase in insecticide-treated net coverage has also slowed since 2014. Less than half of households in sub-Saharan Africa have enough nets for all occupants.

MAHARRA HUSSAIN, *Dubai, United Arab Emirates*

Unregulated sale of unapproved antibiotics in India and emerging antimicrobial resistance

Multinational companies (MNCs) continue to produce and sell unapproved antibiotics in India, though the sale of unapproved medicines is illegal. India has the highest sale of antibiotics and rates of consumption in the world. WHO has emphasized that global efforts are needed to restrict the production and use of unapproved medicines and to limit antimicrobial resistance. Superbugs or highly resistant bacteria are a constantly emerging global threat and are largely due to irrational and rampant use of antibiotics.

A recent study (McGettigan *et al*. Threats to global antimicrobial resistance control: Centrally approved and unapproved antibiotic formulations sold in India. *Br J Clin Pharmacol*, published online 21 Feb 2018, doi: 10.1111/bcp.13503) shows that MNCs continue to manufacture many unapproved formulations, despite pledging to tackle rising antimicrobial resistance. Their team of researchers from India and the UK have discovered that every year millions of unapproved antibiotic units are being sold in India.

The data are alarming—118 different formulations of fixed-dose combinations (FDCs) are being sold in India compared with just 5 in the UK and the USA. Of these 118 formulations, 64% were not approved by the Central Drugs Standard Control Organization (CDSCO). MNCs manufactured 53 of the 118 FDCs; 20 of these were not approved in India, only 4 were approved in the UK and the USA. FDCs are known to generate resistance.

In contrast to the FDCs, 93% of the 86 single-drug formulation (SDF) antibiotics in the market in India have regulatory approval. According to a February 2016 report on antimicrobial resistance commissioned by the then UK Prime Minister David Cameron, failure to act on drug-resistant infections will lead to 10 million extra deaths every year and can cost the global economy US$ 100 trillion by 2050. As much as 27% of the 36% rise in worldwide consumption of antibiotics was observed in the five BRICS countries (Brazil, Russia, India, China and South Africa) between 2000 and 2010. This decade-long study also found that among all the five BRICS countries, 23% increase in the volume of retail sales of antibiotics observed was attributable to India.

Earlier, in India, the researchers (McGettigan *et al*. Use of fixed dose combination [FDC] drugs in India: Central regulatory approval and sales of FDCs containing non-steroidal anti-inflammatory drugs [NSAIDs], metformin, or psychotropic drugs. *PLoS Med* 2015;12) analysed the regulatory records of antibiotics as well as their sales data for the years 2007–2012. The analysis included information on FDC and SDF antibiotics available in the market. The study also analysed the availability of antibiotics and their status of approval.

These studies raise serious questions about the commitment of multinational pharmaceutical companies to the use of appropriate antibiotics. Some explanation is expected from the MNCs as also immediate action against them by the regulatory authorities. Surprisingly, many MNCs are based in the USA. One wonders why these MNCs circulate these unapproved FDCs in India and other lower or low-middle-income countries, but not in the developed world?

The study also raises concerns about unauthorized, unapproved, unregulated antibiotic use in India, which is already burdened with poor healthcare infrastructure, a weak regulatory enforcement and high antibiotic use as well as with one of the highest rates of antibiotic resistance in the world. The 59th Parliamentary Standing Committee Report (2012) referred to the lack of competence in regulating and monitoring drug sales in India. Antimicrobial combinations in circulation require strict approval and cautious use.

JYOTI PRIYADARSHINI SHRIVASTAVA,
Gwalior, Madhya Pradesh