



### DRUG TRIALS

#### Corona Virus Disease (COVID-19) Drug Trials

Till date, there is no definitive treatment for Corona Virus disease (COVID-19). However, there are some ongoing trials that might prove effective for the treatment of COVID-19.

##### Remdesivir

Most likely the most promising treatment. Remdesivir is an adenosine analogue that incorporates into nascent viral RNA chains and results in its pre-mature termination, thereby inhibits RNA synthesis.<sup>1</sup> COVID-19 virus belongs to a corona virus family where SARS (Severe acute respiratory syndrome) & MERS (Middle East respiratory syndrome)<sup>1</sup> also belong, which is enveloped, single-stranded, positive-strand RNA viruses.<sup>2</sup> Remdesivir trials are taking place among adult patients with severe, mild and moderate novel Coronavirus (2019-nCoV) respiratory disease in China which are expected to end by April.<sup>3,4</sup> Another trial on Remdesivir is being done in 50 sites globally in hospitalized adult patients diagnosed with COVID-19.<sup>5</sup>

##### Chloroquine and Hydroxychloroquine

These anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug as it block virus infection by

increasing endosomal pH required for virus/cell fusion.<sup>1</sup> The clinical trial on efficacy and safety of Hydroxychloroquine for treatment of pneumonia caused by 2019-nCoV (HC-nCoV) is being done in China and in UK, Chloroquine is being tested among healthcare workers, or other individuals at significant risk for prevention of coronavirus disease (COVID-19) in the healthcare setting (COPCOV).<sup>6,7</sup> One of the studies done in vitro have recommended that a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance.<sup>8</sup>

##### Lopinavir and Ritonavir

This combination was found to be useful in SARS in vitro.<sup>9</sup> However, randomized, controlled, open-label trial involving 199 hospitalized adult patients with confirmed SARS-CoV-2 infection concluded that no benefit was observed with lopinavir-ritonavir treatment beyond standard care.<sup>10</sup> Several trials are underway with the earliest result expected in May 2020.<sup>11</sup>

##### Ribavirin and Sofosbuvir

Anti-HCV (Hepatitis C virus) drugs Ribavirin and sofosbuvir appeared to be effective in vitro against COVID-19 RNA dependent RNA polymerase (RdRp).<sup>12</sup> Phase 2 trial is going on Ribavirin.<sup>13</sup>

## Interferon beta

It has been shown to be protective among mice infected with MERS-CoV infection and it is hoped that it may have a similar effect in humans with COVID-19 too.<sup>14</sup>

## Tocilizumab

It is a IL-6 receptor antagonist which inhibit inflammatory response. It was used empirically in 48 patients with severe COVID-19 cases in China and strongly suggested that cytokine IL-6 should be considered as a therapeutic target in critically ill patients with excessive inflammatory response.<sup>15</sup>

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**MEDICINE SAFETY****Safety of Prescribing Opioids in Pediatrics: An Update**

Opioid group of drugs are used in achieving adequate pain control in various disease states like cancer, acute illness, peri-operative pain and post-operative pain in pediatric population because of their analgesic properties. Codeine is not only used to treat mild to moderate pain but also to suppress cough. Tramadol is a prescription medicine for treating moderate to moderately severe pain. Tramadol and codeine both are frequently combined with other medicines like acetaminophen as an over-the-counter medication for cough and cold. However, use of such analgesics in the pediatric population is a major concern because of its adverse effects.

The risk of serious breathing problems with the use of both codeine and tramadol is seen in some children who metabolize codeine and tramadol much faster than usual (rapid metabolizers). Rapid metabolization of these drugs lead to increased levels of the active metabolites in the body which give rise to complications of opioid overdose such as respiratory depression, over sedation and death.<sup>1</sup>

In 2013, the FDA had issued a black box warning cautioning the use of codeine in children to relieve pain after tonsillectomy or adenoidectomy because of the risk of respiratory depression.<sup>2</sup> Despite this, studies showed that codeine was

still prescribed in 1 out of 20 pediatric patients undergoing adenotonsillectomy after which updated warnings that were more restrictive were issued in 2015. It contraindicated the use of codeine for pain or cough in children younger than 12 years.<sup>3</sup> Similarly, the use of tramadol in children was contraindicated citing the risk of respiratory depression. Also, use of codeine by breastfeeding mothers posed serious risk of breathing problems in breastfed infants. However, there is no such similar reports regarding tramadol but since tramadol is also secreted in the breast milk, it is assumed that tramadol also share same risks associated with ultra-rapid metabolism as codeine.<sup>4</sup>

Later in 2017, FDA updated their warnings regarding use of codeine and tramadol in pediatric population. It contraindicated the use of codeine to treat pain or cough and tramadol to treat pain in children younger than 12 years. Tramadol use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids was also contraindicated. Currently a new warning to the drug labels of codeine and tramadol was issued which recommended they are not to be used in adolescents between 12 and 18 years who are obese or have conditions like obstructive sleep apnea or severe lung disease. A strengthened warning was also issued for their use in breastfeeding mothers to avoid potential risk of serious adverse reactions to breastfed infants.<sup>5,6</sup>

In our context, Department of Drug Administration has also warned health care professionals about the risk of serious

respiratory depression with the use of codeine, dihydrocodeine and tramadol.<sup>7</sup>

Alternatively, non-opioid analgesics like acetaminophen alternating with ibuprofen can be used for initial pain management. If the combination is not effective, opioids such as oxycodone and hydrocodone can be considered.<sup>1</sup>

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We express our deepest condolence on untimely demise of our coworker Gopal Shrestha. He was very much instrumental in providing IT support to our newsletter. He will be greatly missed. May the departed soul rest in eternal peace.

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