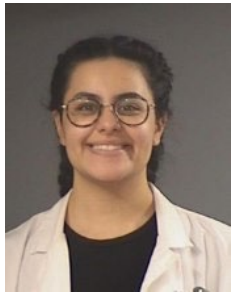
MISCONCEPTIONS OF ALTERNATIVE TREATMENTS FOR COVID AND THEIR TOXICOLOGICAL CONSEQUENCES

RHONDA ABOUELELA, PHARMD

PGY1 PHARMACY RESIDENT

ATLANTIC HEALTH SYSTEM

RHONDA.ABOUELELA@ATLANTICHEALTH.ORG



PRECEPTORS: DEBORAH BOOTH, PHARMD, MS, BCPS, AND FRANK DIAZ, PHARMD BCPS

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OBJECTIVES FOR PHARMACISTS AND NURSES

Recall	Recall the toxicological manifestations associated with the use of hydroxychloroquine, ivermectin and colchicine for the treatment of COVID
Recognize	Recognize the guideline recommendations for the use of hydroxychloroquine, ivermectin and colchicine for use in the treatment and prevention of COVID
Identify	Identify counseling strategies for patients on the risks associated with off-label COVID treatments

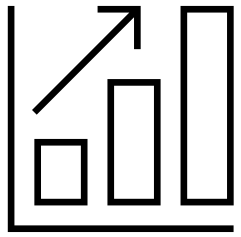
OBJECTIVES FOR PHARMACY TECHNICIANS

Recognize	Recognize agents commonly used in off-label COVID treatment which put a patient at risk for toxic manifestations
Recall	Recall appropriate indications for hydroxychloroquine, ivermectin and colchicine
Identify	Identify counseling strategies for patients on the risks associated with off-label COVID treatments

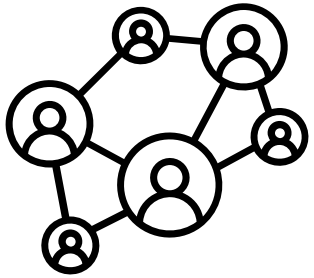
ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)	**SLE**	Systemic lupus erythematosus	**PCR**	Polymerase chain reaction
AE	Adverse event	**F**	Fahrenheit	**PEP**	Post-exposure prophylaxis
AV	Atrioventricular	**FDA**	Food and Drug Administration	**P-gp**	P- glycoprotein
AZM	Azithromycin	**GABA**	Gamma-aminobutyric acid	**PrEP**	Pre-exposure prophylaxis
C	Celsius	**GI**	Gastrointestinal	**PO**	Per os (orally)
CI	Confidence interval	**HCQ**	Hydroxychloroquine	**QTc**	QT corrected
COVID	Coronavirus disease	**HIV**	Human immunodeficiency virus	**RNA**	Ribonucleic acid
CYP	Cytochrome P450	**IV**	Intravenous	**SARS-CoV-2**	Severe acute respiratory syndrome coronavirus 2
DNA	Deoxyribonucleic acid	**mg**	milligrams	**VA**	Ventricular arrythmia
DPV	Division of Pharmacovigilance	**mL**	Milliliters	**VF**	Ventricular fibrillation
DSC	Drug Safety Commission	**OR**	Odds ratio	**VT**	Ventricular tachycardia
EKG ECG	Electrocardiogram	**PETAL**	Prevention and Early Treatment of Acute Lung Injury	**WHO**	World Health Organization
EUA	Emergency use authorization				

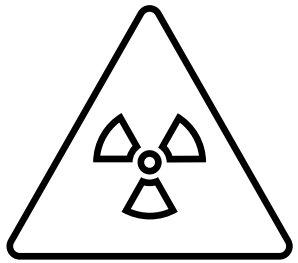
OVERDOSES/TOXICITY RELATED TO COVID SELF-TREATMENT



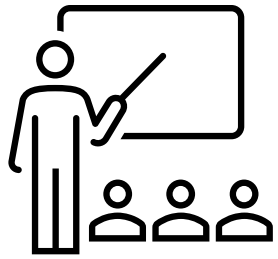
With the rise of COVID since December of 2019, there has been an associated increase in the inappropriate use of medications intended to treat the disease



Misinformation regarding potential COVID treatments has led to surges of toxicity with several agents, leading to moderate-to-severe poisonings/overdoses



Agents like hydroxychloroquine, ivermectin, and colchicine have been reported to be the cause of many toxicities since the beginning of the pandemic



The purpose of the presentation is to review the appropriate uses of these medications, define their place in COVID therapy, and discuss the dangers of toxicity associated with each agent

SOURCES: WONG A. EMERG MED AUSTRALAS. 2020
CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021
AHMAD AR, ET AL.. J MED INTERNET RES. 2020

COVID OVERVIEW

- Respiratory disease caused by SARS-CoV-2, a coronavirus discovered in 2019 originating in Wuhan, China
- Highly contagious and globally devastating, quickly becoming a massive pandemic
- Early stages of disease spread since December of 2019 were accompanied with widespread panic and communities looking for any form of protection, prevention, and treatment
- **Globally**, as of **March 25th, 2022,** there have been **476,374,234 confirmed cases** of COVID-19, including **6,108,976 deaths,** reported to the World Health Organization

SOURCES: CDC. CORONAVIRUS DISEASE 2019 (COVID-19).
WHO CORONAVIRUS (COVID-19) DASHBOARD. WHO (COVID-19) HOMEPAGE.

HOW SOCIAL MEDIA CREATES MISCONCEPTIONS

Prior to the outbreak of COVID, many people already relied on social media for news

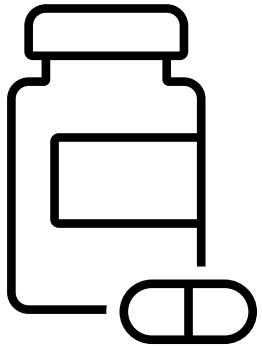
In the early months of 2020, while the pandemic began to surge, information about COVID was rapidly published and shared through social media sites

Social media plays a significant role in spreading fear and panic in times of crisis, creating a social media *infodemic*

- Infodemic: an excessive amount of information about a problem that is typically unreliable, spreads rapidly, and makes a solution more difficult to achieve

Anxiety about severity of disease and lack of approved treatment options lead to encouragement of inappropriate treatment and preventative alternatives and subsequent widespread drastic measures to prevent or treat COVID

SOURCE: AHMAD AR, ET AL.. J MED INTERNET RES. 2020



HYDROXYCHLOROQUINE
CHLOROQUINE

HYDROXYCHLOROQUINE

- **Mechanism**
  - Binds to and inhibits DNA and RNA polymerase
  - Accumulation increases internal pH, which inhibits antigen processing
  - Inhibits prostaglandin effects/inflammatory response
- **FDA approved indications**
  - Malaria
  - Systemic lupus erythematosus (SLE)
  - Rheumatoid arthritis (RA)
- **Drug interactions**
  - Mild CYP2D6 and P-glycoprotein inhibitor, may decrease antiviral effects of remdesivir
  - Caution with other QT prolonging agents
- **Typical dosing**
  - RA/SLE
    - 200-400 mg PO daily as a once or twice daily divided dose
  - Malaria
    - 800 mg PO once, followed by 400 mg at 6, 24, and 48 hours after initial dose (total dose: 2 g)
- **Metabolism**
  - Hepatic (alkylation and glucuronidation) and renal metabolism
  - Half-life:15-31 hours
- **Elimination**
  - 15-25% renal (up to 60% as unchanged drug)

SOURCE: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022

HYDROXYCHLOROQUINE

- **Side effects**
  - Dizziness, fatigue, weakness
  - Headache
  - Anxiety, excitability
  - Loss of appetite, weight loss
  - GI disturbances
  - Change in skin and hair color
  - Hair loss
- **Formulations**
  - 100-400 mg oral tablets
- **Storage**
  - Store at room temperature, up to 30°C (86°F)
  - Keep in a dry location
  - Protect from light

SOURCE: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022

CHLOROQUINE

- **Mechanism**
  - Binds to and inhibits DNA and RNA polymerase
  - Accumulation increases internal pH, which inhibits antigen processing
  - Inhibits prostaglandin effects/inflammatory response
- **FDA approved indications**
  - Malaria
  - Extraintestinal amebiasis
- **Drug Interactions**
  - Caution with other QT prolonging agents
- **Typical dosing**
  - Malaria: 1 gram PO day one followed by 500 mg 6, 24, and 48 hours after first dose
  - Extraintestinal amebiasis: 1 gram PO daily x2 days, followed by 500 mg PO daily for at least 2-3 weeks
- **Metabolism**
  - Partially hepatic
  - Half-life
    - ~75 hours in healthy patients
    - ~200 hours in chronic renal insufficiency
- **Elimination**
  - ~70% renal (~35% eliminated as unchanged drug)

SOURCE: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022

CHLOROQUINE

- **Side effects**
  - Restlessness/insomnia
  - Seizures
  - Mood/behavioral changes
  - Confusion/hallucinations
  - Auditory complications
  - Myopathy
  - Hepatotoxicity
  - Arrythmia
  - Skin reactions
  - Hypoglycemia

- **Formulations**
  - 250 mg and 500 mg oral tablets

Veterinary/aquarium formulations (*off-label use)
- Chloroquine phosphate pellets, flakes, powder, tablets intended for fish
- Not interchangeable with human products

- **Storage**
  - Store at room temperature, up to 30°C (86°F)
  - Keep in a dry location
  - Protect from light

SOURCES: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022
FDA LETTER TO STAKEHOLDERS: DO NOT USE CHLOROQUINE PHOSPHATE INTENDED FOR FISH AS TREATMENT FOR COVID-19 IN HUMANS. 2020

PROPOSED MECHANISM/BENEFIT IN COVID

*OFF-LABEL USE

- Both hydroxychloroquine and chloroquine have activity against SARS-CoV-2 ***in vitro***
  - *In vitro* studies in early 2020 suggested dosing regimens for COVID based on physiologically-based pharmacokinetic models

Small cohort study investigating hydroxychloroquine suggested that use may reduce risk of COVID transmission

- **No control group** ★

SOURCES: YAO X, ET AL. CLIN INFECT DIS. 2020
VINCENT MJ, ET AL. VIROL J. 2005

March 28, 2020

FDA authorized the emergency use of hydroxychloroquine and chloroquine to treat patients hospitalized with COVID for whom participation in clinical trial is not available

April 24, 2020

FDA issued a Drug Safety Communication (DSC) **cautioning against the use of hydroxychloroquine or chloroquine for COVID** outside of the hospital setting or a clinical trial **due to risk of arrhythmias**. The DSC described reports of serious cardiac events, including QT prolongation, in patients receiving hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines, for the prevention or treatment of COVID

April 13, 2020

Division of Anti-infective products opened a priority Tracked Safety Issue to assess the risk of cardiac toxicity with hydroxychloroquine and chloroquine with or without azithromycin when used for the treatment of COVID

May 6, 2020

Division of Applied Regulatory Science and Division of Pharmacovigilance (DPV) opened a Newly Identified Safety Signal to track an emerging signal of methemoglobinemia with hydroxychloroquine in the setting of COVID

SOURCES: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (PHARMACOVIGILANCE MEMORANDUM), MAY 19,2020

MANIFESTATIONS OF TOXICITY

- **Mild toxicities:** GI disturbances, hallucinations, weakness
- **Severe toxicities:** EKG changes including QTc prolongation, AV block, altered mental status or delirium, seizures
- **Life threatening toxicities:** respiratory depression, electrolyte disturbances, cardiac dysrhythmias

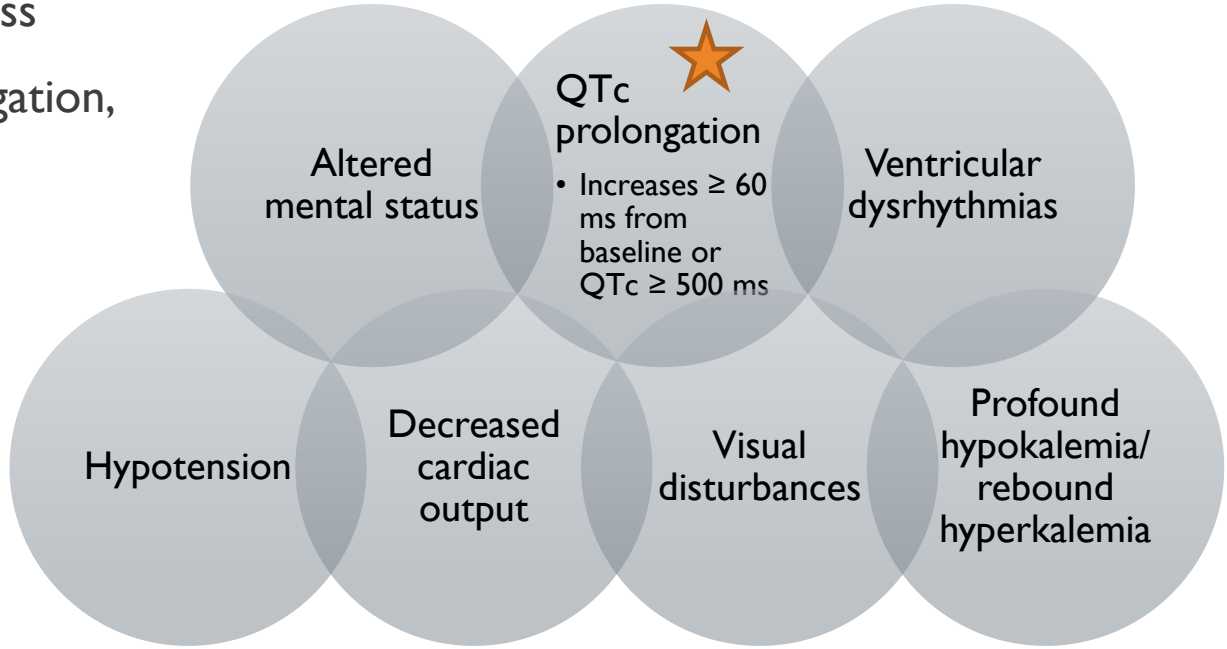


Table 4. All Hydroxychloroquine and Chloroquine Cases Reporting Adverse Events in the Setting of COVID-19 from December 1, 2019-May 6, 2020 (n=385)

	Hydroxychloroquine (n=347)	Chloroquine (n=38)
Fatal Cases	77	10

SOURCES: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022
BAKHSH HT. J MICROSC ULTRASTRUCT. 2020
DE OLANO J, ET AL. AM J EMERG MED. 2019
MARQUARDT K, ALBERTSON TE. AM J EMERG MED. 2001
DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (PHARMACOVIGILANCE MEMORANDUM), 2020

- Most frequently reported dose was 400 mg/day (43%)
  - Consistent with labeled dosing
- Of 256 reported hydroxychloroquine or chloroquine doses:
  - 6 for prophylaxis of COVID
  - 250 for treatment of COVID

Table 5. Possibly/Probably Associated Hydroxychloroquine and Chloroquine Cases Reporting Serious Adverse Events in the Setting of COVID-19 from December 1, 2019-May 6, 2020 (n=211)*

	Hydroxychloroquine	Chloroquine
Serious Cardiac AEs	**(n=90)**	**(n=19)**
Labeled Cardiac AEs*	(n=85)	(n=19)
QT prolongation	62	18
VA, VF, VT	11	3
Bradycardia	7	1
Tachyarrhythmia	4	0
Tachycardia (excluding VT, tachyarrhythmia)	4	0
Torsades de Pointes	4	0
AV block	3	1
Arrythmia (excluding VA, VF, VT, tachyarrhythmia)	3	0
QRS prolongation	2	1
Cardiovascular collapse (in overdose)	1	0
Unlabeled AEs*	(n=5)	(n=0)
Atrial fibrillation/atrial flutter	4	0
Myocardial infarction	1	0
Concomitant Treatments of Interest	(n=76)	(n=16)
Azithromycin	55	12
Lopinavir/ritonavir	5	0
Azithromycin+ Lopinavir/ritonavir	7	1
Other QT prolonging drugs	24	3
Fatal Cardiac Cases#	17	8

Abbreviations: AE = adverse event, VA = ventricular arrhythmia, VF = ventricular fibrillation, VT = ventricular tachycardia, AV = atrioventricular

* A case may have more than one AE. Some cases reported both a cardiac and non-cardiac AE. The FDA reviewer assessed the reported AEs were probably/possibly associated with hydroxychloroquine or chloroquine use

Fatal cardiac cases are considered those cases reporting death and a cardiac AE. Cases were not individually evaluated to determine if the cardiac AE was the cause of death.

SOURCES: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (PHARMACOVIGILANCE MEMORANDUM), 2020

TOXICITY MANAGEMENT: KEY POINTS

Frequent monitoring of vitals and mental status

- Frequent EKG or continuous telemetry monitoring

Symptomatic management

- Airway protection, hemodynamic support, etc.

Avoid QT prolonging medications for nausea/vomiting

- 5HT3 antagonists
- Dopamine

Avoid class 1A, IC, III antiarrythmics

Consider decontamination in early ingestion (1-2 hours post-ingestion)

SOURCES: DELLA PORTA A, ET AL. AM J EMERG MED. 2020
DE OLANO J, ET AL. AM J EMERG MED. 2019
MARQUARDT K, ALBERTSON TE. AM J EMERG MED. 2001

NIH GUIDELINE RECOMMENDATIONS

*OFF-LABEL USE

Pre-exposure prophylaxis

- The Panel recommends against the use of any oral drugs for SARS-CoV-2 PrEP, except in a clinical trial
- Clinical trials are investigating several agents including hydroxychloroquine and ivermectin

Post-exposure prophylaxis

- The Panel recommends against the use of hydroxychloroquine for SARS-CoV-2 PEP

Treatment

- The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin, lopinavir/ritonavir, and other HIV protease inhibitors for the outpatient treatment of COVID-19
- The Panel recommends against the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in hospitalized patients and in non-hospitalized patients

SOURCE: CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021

LITERATURE

*OFF-LABEL USE

Hospitalized patients

- RECOVERY trial
  - HCQ did not show decrease of 28-day mortality vs. standard of care
  - Patients receiving HCQ had longer median length of stay, and were more likely to be intubated or die during hospitalization
- Solidarity trial and PETAL trial both halted early due to futility

Non-Hospitalized patients

- Mitjà O et al.
  - HCQ vs no antiviral therapy for 307 non hospitalized patients
  - No detectable difference in average reduction of SARS-CoV-2 RNA at Day 3 or the time to clinical improvement between the two groups

SOURCES: CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021
MITJÀ O, ET AL., N ENGL J MED. 2021
SELF WH, ET AL. JAMA. 2020
RECOVERY COLLABORATIVE GROUP, HORBY P, ET AL. N ENGL J MED. 2020
WHO SOLIDARITY TRIAL CONSORTIUM, PAN H, ET AL. N ENGL J MED. 2021

HYDROXYCHLOROQUINE WITH OR WITHOUT AZITHROMYCIN

*OFF-LABEL USE

Association of Treatment With Hydroxychloroquine (HCQ) or Azithromycin (AZM) With In-Hospital Mortality in Patients With COVID-19 in New York State	
Design/ Objective	Retrospective, multicenter, observational study investigating association between use of HCQ, with or without AZM, and in-hospital mortality in patients diagnosed with COVID
Population	Random sample of hospitalized adults with COVID-19 from the New York Department of Health (n = 1,438)
Interventions	• HCQ+ AZM (n=735) • HCQ alone (n=271) • AZM alone (n=211) • Neither drug (n=221)

Outcomes/ Conclusions	• Primary Endpoint: In-hospital mortality
	  • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug
	• Secondary Endpoint: Cardiac arrest and arrhythmia or QT prolongation on an ECG
	  • Patients who received HCQ + AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05)

SOURCE: ROSENBERG ES, ET AL. JAMA. 2020

FDA WARNING FOR CHLOROQUINE

*OFF-LABEL USE

On **March 27th, 2020**, the **FDA's Center for Veterinary Medicine** posted a warning about human use of chloroquine phosphate that is intended for aquarium fish

United States couple took chloroquine phosphate that was used to treat their fish, in attempts to prevent COVID infection

Resulted in severe illness of wife and death of husband

FDA LETTER TO STAKEHOLDERS: DO NOT USE CHLOROQUINE PHOSPHATE INTENDED FOR FISH AS TREATMENT FOR COVID-19 IN HUMANS. 2020

FDA GUIDANCE

*OFF-LABEL USE

June 15, 2020 Update:

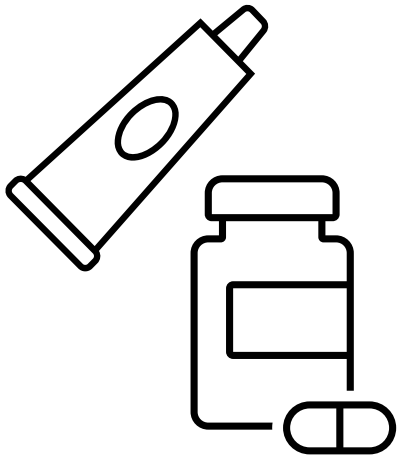
- FDA revoked the emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when a clinical trial is unavailable or participation is not feasible. We made this determination based on recent results from a large, randomized clinical trial in hospitalized patients that found these medicines showed no benefit for decreasing the likelihood of death or speeding recovery

SOURCES: FDA. FDA CAUTIONS AGAINST USE OF HYDROXYCHLOROQUINE OR CHLOROQUINE FOR COVID-19 OUTSIDE OF THE HOSPITAL SETTING OR A CLINICAL TRIAL DUE TO RISK OF HEART RHYTHM PROBLEMS. FDA WEBSITE.,2020.

HYDROXYCHLOROQUINE/CHLOROQUINE: KEY COUNSELING POINTS

*OFF-LABEL USE

- Hydroxychloroquine and chloroquine are NOT recommended for prevention or treatment of COVID
- Cardiac toxicological manifestations are a main source of concern
- Risk of arrythmia can be worsened by concomitant use of additional QT prolonging agents
- Veterinary/aquarium formulations of chloroquine are not interchangeable with human formulations



IVERMECTIN

IVERMECTIN

- **Mechanism**
  - Selectively binds with strong affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells
  - Leads to increased permeability of cell membranes to chloride ions and subsequent hyperpolarization of the nerve or muscle cell
- **FDA approved indications**
  - Onchocerciasis
  - Intestinal strongyloidiasis
- **Drug interactions**
  - No relevant drug interactions
- **Typical dosing**
  - 150-400 mcg/kg/dose every 7 days
  - Duration dependent on indication
- **Metabolism**
  - Hepatic via CYP3A4 (major), CYP2D6 (minor), and CYP2E1 (minor)
  - Half-life: 18 hours
- **Elimination**
  - Feces/urine (<1%)

SOURCE: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022

IVERMECTIN

- **Side effects**
  - Lightheadedness/syncope
  - Changes in eyesight, eye pain, eye irritation
  - Itching/skin irritation
  - Joint pain
  - Edema
  - Fever
- **Storage**
  - Store at room temperature, up to 30°C (86°F)
  - Keep in a dry location

- **Formulations**
  - 3 mg oral tablets
  - 0.5-1% topical lotions/creams

Veterinary formulations (*off-label use)
- Can be highly concentrated
- 1.87% paste
- 1% solution for injection
- "Sheep drench" or "pour-on" for cattle **(5 mg/mL)**

SOURCES: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022
CDC. EMERGENCY PREPAREDNESS AND RESPONSE.. 2021.
DURVET. HOMEPAGE ON THE INTERNET. 2022

PROPOSED MECHANISM/BENEFIT IN COVID

*OFF-LABEL USE

Reports from *in vitro* studies

- Ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins
- Necessary for key intracellular transport process that viruses hijack to suppressing the host's antiviral response
- Additionally, docking may interfere with the attachment of the SARS-CoV-2 spike protein to the human cell membrane

Ivermectin is thought to be a host-directed agent

- May be the basis for its broad-spectrum activity *in vitro* against the viruses that cause dengue, Zika, HIV, and yellow fever

Despite this *in vitro* activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses.

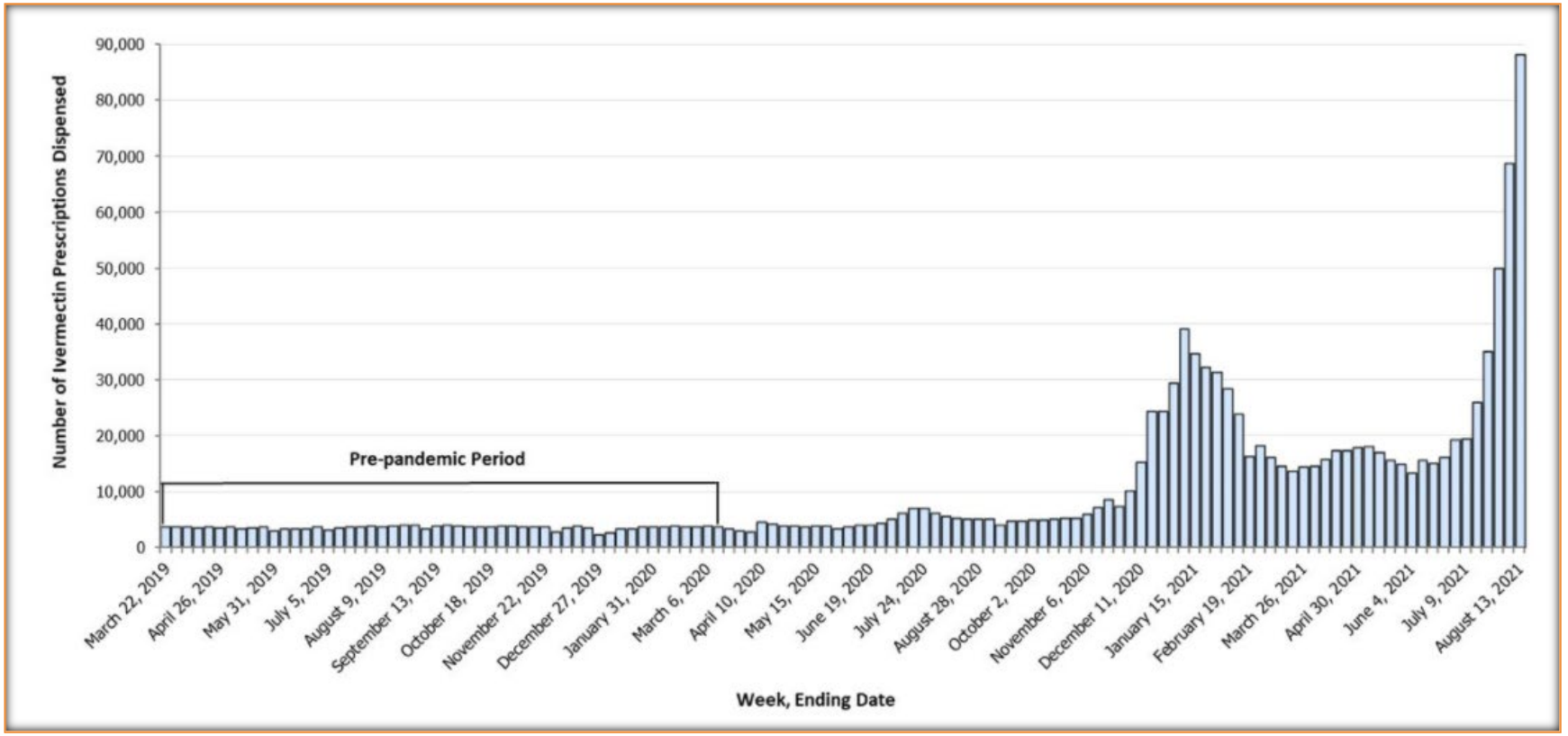
- Plasma concentrations necessary for antiviral efficacy found *in vitro* would require doses ~100x higher than approved dosing for human use

Some studies of ivermectin have report potential anti-inflammatory properties

- Suspected to be beneficial in COVID

SOURCES: CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021

ESTIMATED NUMBER OF OUTPATIENT IVERMECTIN PRESCRIPTIONS DISPENSED FROM RETAIL PHARMACIES — UNITED STATES, MARCH 16, 2019–AUGUST 13, 2021



SOURCE: CDC. EMERGENCY PREPAREDNESS AND RESPONSE. 2021

TOXICITY REPORTS

"Poison Control Centers Are Fielding A Surge Of Ivermectin Overdose Calls"

- September 2021

"Poison control centers are seeing a dramatic surge in calls from people who are self-medicating with ivermectin, an anti-parasite drug for animals that some falsely claim treats COVID-19"

National Poison Data System, which collects information from the nation's 55 poison control centers, reported a 245% increase in reported exposure cases of ivermectin from July to August 2021-from 133 to 459

- 1,143 ivermectin exposure cases were reported between January 1 and August 31, 2021
- 163% increase over the same period in 2020

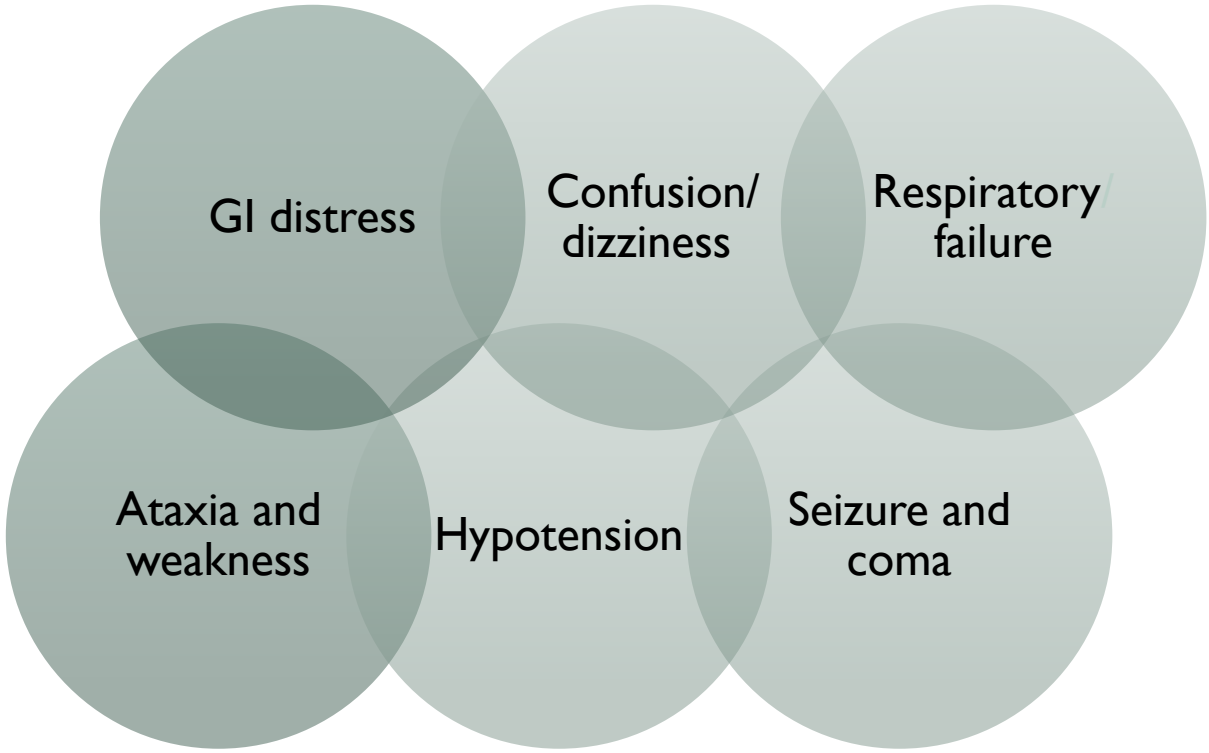
Most patients are overdosing on a veterinary formulations of drug intended for cows and horses

- Number of prescriptions for use by humans in the United States is 24x more than before the pandemic

ROMO V. CORONAVIRUS UPDATES. NPR.ORG.2021
FDA. CONSUMER UPDATES. WHY YOU SHOULD NOT USE IVERMECTIN TO TREAT OR PREVENT COVID-19. FDA WEBSITE. 2022

MANIFESTATIONS OF TOXICITY

- Symptoms developed in most persons within 2 hours after a large, single, first-time ingestion
- Reported doses by Oregon Poison center from August 2021:
  - Veterinary products: 6.8-125 mg of 1.87% paste and 20-50 mg of 1% solution
  - Tablets for human use: 21 mg per dose, twice weekly for prevention
- Uncontrolled aspiration may complicate recovery



SOURCES: TEMPLE C, ET AL. N ENGL J MED. 2021
CHUNG K, ET AL. ANN EMERG MED. 1999

IVERMECTIN TOXICITY MANAGEMENT: KEY POINTS

Largely supportive care

- Symptom management, airway protection, hemodynamic support, etc.

Consider decontamination in early ingestion (1-2 hours post-ingestion)

Avoid benzodiazepines

- Ivermectin can affect GABA receptors

SOURCE: CHUNG K, ET AL. ANN EMERG MED. 1999

NIH GUIDELINE RECOMMENDATIONS

*OFF-LABEL USE

Pre-exposure prophylaxis

- The Panel recommends against the use of any oral drugs for SARS-CoV-2 PrEP, except in a clinical trial
- Clinical trials are investigating several agents including hydroxychloroquine and ivermectin

Post-exposure prophylaxis

- The Panel recommends against the use of ivermectin for SARS-CoV-2 PEP, except in a clinical trial

Treatment

- There is insufficient evidence for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19
- Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19

SOURCE: CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021

LIMITATIONS OF CURRENT IVERMECTIN LITERATURE FOR TREATMENT OF COVID

*OFF-LABEL USE

- Small sample size
- Variations in ivermectin regimens (dosing and frequency)
- Some randomized controlled trials were open-label
- Patients received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, corticosteroids)
- COVID severity study participants was not consistently well described
- Study outcome measures were not always clearly defined

I-TECH RANDOMIZED CLINICAL TRIAL

*OFF-LABEL USE

Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities	
Design/ Objective	• Open-label randomized clinical trial investigating if ivermectin shows prevention of progression to severe disease among high-risk patients with COVID • 20 public hospitals and a COVID quarantine center in Malaysia • From May 31, 2021- October 25, 2021
Population	• Inclusion: Confirmed COVID, ≥ 50 years old, at least 1 comorbidity, presenting with mild-moderate illness within 7 days of symptom onset • Exclusion: Asymptomatic, required supplemental oxygen, or had pulse oximetry oxygen saturation (SpO_2) level less than 95% at rest
Cohorts	• Ivermectin 0.4 mg/kg PO daily x 5 days + standard of care (n=241) • Standard of care alone (n=249)
Outcomes	• Primary outcome: proportion of patients who progressed to severe disease (defined as the hypoxic stage requiring supplemental oxygen to maintain pulse oximetry oxygen saturation of 95% or higher) • 52 of 241 patients (21.6%) in the ivermectin group and 43 of 249 patients (17.3%) in the control group progressed to severe disease (relative risk [RR], 1.25; 95% CI, 0.87-1.80; *P* = .25) • Secondary outcomes: rates of mechanical ventilation, intensive care unit admission, 28-day in-hospital mortality, and adverse events: no significant differences between groups
Conclusions	Ivermectin treatment during early illness did not prevent progression to severe disease

SOURCE: LIM SCL, ET AL. JAMA INTERN MED. 2022

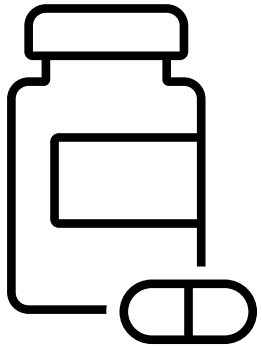
IVERMECTIN: KEY COUNSELING POINTS

*OFF-LABEL USE

Veterinary formulations of drug are not for human use

High dose ingestions are associated with potentially severe clinical complications and toxicity

Current clinical trials underway to more clearly define place in therapy



COLCHICINE

COLCHICINE

- **Mechanism**
  - Inhibits microtubule function, preventing activation, degranulation, and migration of neutrophils. May interfere with activation of interleukin-1β (immunomodulator)
- **FDA approved indications**
  - Gout Flares
- **Drug interactions**
  - No relevant drug interactions
- **Dosing**
  - 0.6 mg once or twice daily
- **Metabolism**
  - CYP3A4 and glucuronidation; 3 metabolites (2 primary, 1 minor)
  - Half-life: 27-31 hours
- **Elimination**
  - Urine (40% to 65% as unchanged drug); enterohepatic recirculation

SOURCE: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022

COLCHICINE

- **Side effects**
  - Nausea/vomiting/diarrhea
  - Numbness/tingling in hands or feet
  - Pale skin
  - Myopathy
- **Formulations**
  - 0.6 mg oral tablets
- **Storage**
  - Stored at room temperature, 20-25°C (68-77°F)
  - Keep in a dry location
  - Protect from light

SOURCE: LEXI-DRUGS. HUDSON, OH: LEXICOMP, 2022

PROPOSED MECHANISM/BENEFIT IN COVID

*OFF-LABEL USE

Colchicine has several potential mechanisms, including: reduction of chemotaxis of neutrophils, inhibition of inflammasome signaling and cytokine production

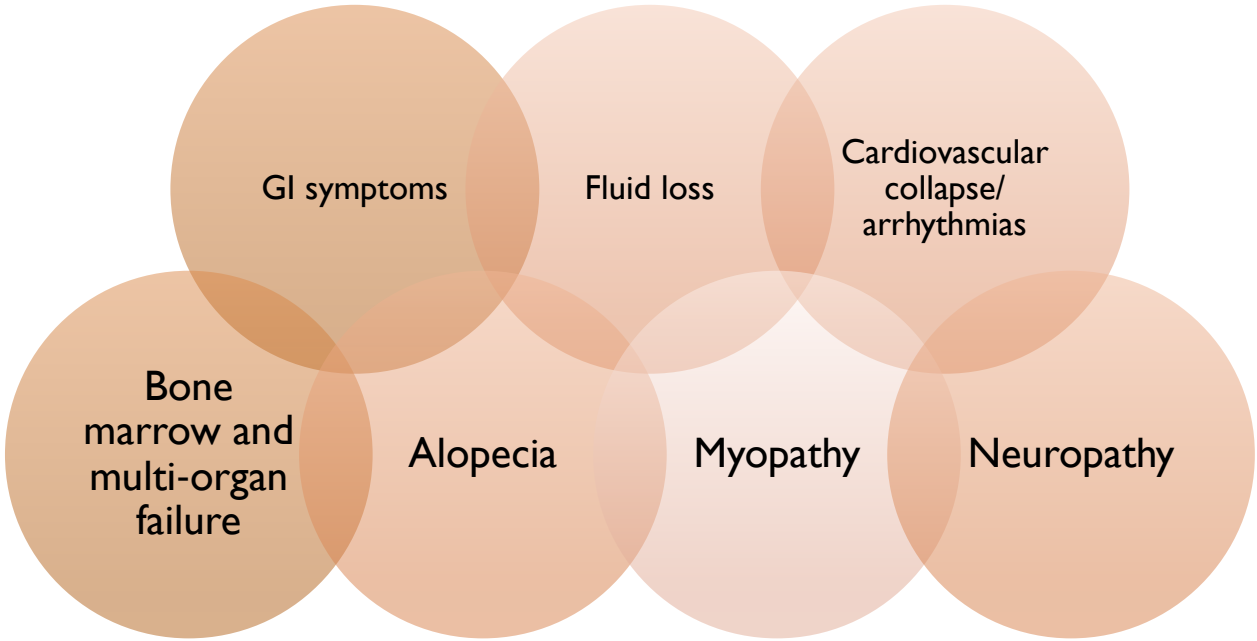
- When colchicine is administered early in the course of COVID-19, these mechanisms could potentially mitigate or prevent inflammatory response

Anti-inflammatory properties, in combination with colchicine's minor immunosuppressive potential and widespread availability has prompted interest and investigation for the treatment of COVID-19

SOURCES: REYES AZ, ET AL. ANN RHEUM DIS. 2021
CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021

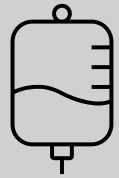
MANIFESTATIONS OF TOXICITY

- Acute toxicity in 3 phases:
  - **0-24 hours:** Nausea, vomiting, diarrhea, leukocytosis
  - **1-7 days:** Sudden cardiac death (24-48 hours), pancytopenia, kidney injury, rhabdomyolysis, electrolyte imbalance, sepsis, acute respiratory distress syndrome
  - **>7 days:** Alopecia, myopathy, neuropathy
- Death results from rapidly progressive multi-organ failure and sepsis



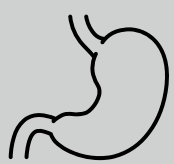
SOURCES: WONG A. EMERG MED AUSTRALAS. 2020
FINKELSTEIN Y, ET AL. CLIN TOXICOL (PHILA). 2010

COLCHICINE TOXICITY MANAGEMENT: KEY POINTS



Largely supportive care

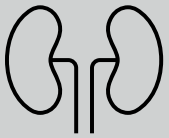
- Symptom management (airway protection, hemodynamic support, etc.)
- Granulocyte colony-stimulating factor



Consider decontamination in early ingestion (1-2 hours post-ingestion)

- <60 mins may warrant gastric lavage

Colchicine is <u>not</u> removable by hemodialysis



Pre-existing renal or liver impairment associated with poor prognosis

SOURCES: FINKELSTEIN Y, ET AL. CLIN TOXICOL (PHILA). 2010
HAYES B. ALIEM. 2021

NIH GUIDELINE RECOMMENDATION

*OFF-LABEL USE

Non-hospitalized patients

The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **colchicine** for the treatment of non-hospitalized patients with COVID-19, except in a clinical trial

Hospitalized patients

The Panel **recommends against** the use of **colchicine** for the treatment of hospitalized patients with COVID-19

SOURCE: CORONAVIRUS DISEASE 2019 (COVID-19) TREATMENT GUIDELINES. NIH. 2021

LITERATURE

*OFF-LABEL USE

Hospitalized patients

- RECOVERY trial:
  - Large randomized trial in hospitalized patients with COVID-19, colchicine showed no benefit in regard to 28-day mortality or any secondary outcomes

Non-hospitalized patients

- COLCORONA trial:
  - Did not reach its primary efficacy endpoint of reducing hospitalizations/death
  - However, in the subset of patients whose diagnosis was confirmed by a positive COVID PCR, slight reduction in hospitalizations was seen in patients who received colchicine.
- PRINCIPLE trial:
  - Colchicine versus usual care
  - Stopped early for futility

SOURCES: TARDIF JC, ET AL. LANCET RESPIR MED. 2021
PRINCIPLE TRIAL COLLABORATIVE GROUP. LANCET. 2021
RECOVERY COLLABORATIVE GROUP. LANCET RESPIR MED. 2021

COLCHICINE: KEY COUNSELING POINTS

*OFF-LABEL USE

Trials comparing colchicine to standard of care have not shown benefit

Colchicine is currently not recommended for prevention or treatment of COVID

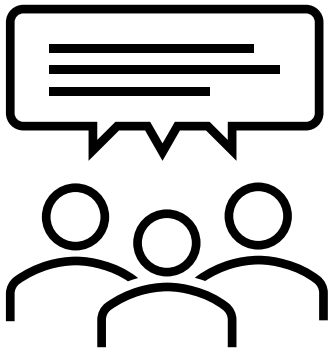
Serious toxicities may develop from acute ingestion of this agent

KEY TAKEAWAYS

Social media can be a great source of health misinformation for the general public in times of crisis/high states of fear

Misinformation regarding ivermectin, hydroxychloroquine, and colchicine, has led to inappropriate use and an increase in avoidable toxicities during the rise of the COVID pandemic

Current literature does not support the use of these therapies for prevention or treatment of COVID



ASSESSMENT

ASSESSMENT QUESTION #1

- Which of the following agents have been reported to be the cause of toxic ingestions/overdoses in the setting of COVID?
  - A. Ibuprofen
  - B. Chloroquine
  - C. Ivermectin
  - D. Both B&C

ASSESSMENT QUESTION #1

- Which of the following agents have been reported to be the cause of toxic ingestions/overdoses in the setting of COVID?

A. Ibuprofen

B. Chloroquine

C. Ivermectin

D. Both B&C

Chloroquine and Ivermectin have both been reported to be associated with toxic reports in the setting of COVID

ASSESSMENT QUESTION #2

- Which of the following is **NOT** an approved/appropriate indication for hydroxychloroquine, ivermectin or colchicine?
  A. Gout
  B. Malaria
  C. Lupus
  D. COVID
  E. Rheumatoid arthritis

ASSESSMENT QUESTION #2

- Which of the following is **NOT** an approved/appropriate indication for hydroxychloroquine, ivermectin or colchicine?

A. Gout

B. Malaria

C. Lupus

D. COVID

E. Rheumatoid arthritis

Currently, none of the above agents are recommended or approved for prophylaxis or treatment of COVID

ASSESSMENT QUESTION #3

- Which of the following signs and symptoms have been reported with ivermectin, colchicine, and hydroxychloroquine toxicity: (select all that apply)
  - A. Gastrointestinal distress
  - B. Hypotension
  - C. Seizures
  - D. Arrythmias

ASSESSMENT QUESTION #3

- Which of the following signs and symptoms have been reported with ivermectin, colchicine, and hydroxychloroquine toxicity: (select all that apply)

A. **Gastrointestinal distress**
B. **Hypotension**
C. **Seizures**
D. **Arrythmias**

A: Ivermectin and colchicine
B: HCQ and ivermectin
C: Ivermectin
D: HCQ (QT prolongation) and colchicine

ASSESSMENT QUESTION #4

- **True/False:** NIH COVID treatment guidelines state that there is insufficient evidence to support the use of ivermectin for COVID treatment and recommends against the use of hydroxychloroquine and colchicine for the treatment of COVID in hospitalized patients (and non-hospitalized for hydroxychloroquine).

ASSESSMENT QUESTION #4

- **True**/False: NIH COVID treatment guidelines state that there is insufficient evidence to support the use of ivermectin for COVID treatment and recommends against the use of hydroxychloroquine and colchicine for the treatment of COVID in hospitalized patients (and non-hospitalized for hydroxychloroquine).

ASSESSMENT QUESTION #5

- For which of the following agents should a pharmacist/nurse/technician counsel a patient on the risk of QTc prolongation? (select all that apply)
  - A. Colchicine
  - B. Hydroxychloroquine
  - C. Ivermectin
  - D. Azithromycin

ASSESSMENT QUESTION #5

- For which of the following agents should a pharmacist/nurse/technician counsel a patient on the risk of QTc prolongation? (select all that apply)

A. Colchicine

B. Hydroxychloroquine

C. Ivermectin

D. Azithromycin

- Hydroxychloroquine, especially in combination with other QT prolonging agents like azithromycin, has been associated with QT prolongation and development of arrythmias
- Ivermectin and colchicine have not been reported to cause QT prolongation

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THANK YOU!!

RHONDA ABOUELELA, PHARMD

PGY1 PHARMACY RESIDENT

RHONDA.ABOUELELA@ATLANTICHEALTH.ORG