COVID-19
Potential Treatments Part 1
Chloroquine and Hydroxychloroquine

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- No relevant financial interests

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Overview

- Situation update
- Pharmaceutical Research 101
- Chloroquine & Hydroxychloroquine

New Mexico 3/25/2020

- https://cv.nmhealth.org/
- 100 cases, 1 death
- Closure of non-essential business
- Measures to preserve NM’s supply of healthcare PPE
  - Prohibits non-essential procedures
  - Prohibits companies and facilities from selling or distributing PPE supplies without DOH approval

US 3/25/2020

- https://www.cdc.gov/coronavirus/2019-nCoV/index.html
- 54,453 cases, 737 deaths (CFR 1.4%)
- New York 26,358
- Washington, California >2000 each

Global 3/25/2020

- https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
- 451,355 cases; 20,459 deaths (CFR 4.5%)
- Germany: 35,740 cases; 186 deaths (CFR 0.5%)
- Italy: 74,386 cases; 7503 deaths (CFR 10%)
- South Korea: 9137 cases; 126 deaths (CFR 1.4%)

Pharmaceutical Research 101

- Does drug *x* work for disease *y*?
- Randomized controlled clinical trial
  - *Clinical* = People
  - *Randomized* = 2 groups of patients who are equivalent at the beginning – “apples to apples”, so at the end, the only difference is the drug
  - *Controlled* = 1 group gets the drug, one group doesn’t
- Statistical significance
  - The results of a study are not merely due to chance
- Clinical significance
  - Translates to direct patient care

Pharmaceutical Research 101

- Clinical significance
  - Translates to direct patient care

Numbers we can measure → Affect on a person's life

Blood pressure → Prevent stroke?

Cholesterol → Prevent heart attack?

Negative nasal swab → Go home from hospital sooner?
Need less oxygen? → Prevent transmission?

Published Research on Chloroquine/ hydroxychloroquine in COVID-19

- 1 letter that alludes to multiple clinical trials
- 2 *in vitro* lab studies
- 1 (deeply flawed) clinical trial

- Many more studies ongoing but have not been published yet

Chloroquine and Hydroxychloroquine

- Chloroquine
  - Malaria treatment and prevention
  - Auto-immune disease Lupus treatment
- Hydroxychloroquine
  - Malaria treatment and prevention
  - Auto-immune diseases Lupus and Rheumatoid Arthritis treatment
  - Multiple other auto-immune diseases
  - Bacterial infection “Q fever” treatment

Notable side effects – FDA Prescriber Information

https://www.drugs.com/pro/chloroquine.html
https://www.drugs.com/pro/hydroxychloroquine-tablets.html

- Overall safe
- Stomach upset, diarrhea – ***common***
- Retina damage
  - High doses for a long time > 5years
- Cardiac toxicity, irregular heartbeat, and heart failure - ***rare***
- + Many more
- Multiple interactions with other drugs
- As little as 2 tablets can be fatal in children

Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies

Gao, J., et.al. Biosci Trends. 2020 Mar 16;14(1):72-73. doi: 10.5582/bst.2020.01047

Gao J., et al.

doi: 10.5582/bst.2020.01047.

- Letter to a journal
- States there are clinical trials from 10 hospitals, > 100 patients
- “Chloroquine phosphate is superior to the control treatment” re:
  - Pnuemonia
  - Lung function
  - CT scan findings
  - Shortening disease course
- “According to the news briefing”

Gao J., et al.

doi: 10.5582/bst.2020.01047.

- “experts from government and regulatory authorities and organizers of clinical trials reached an agreement that chloroquine phosphate has potent activity against COVID-19”

- No other information is given.
  - Actual study design (randomized?)
  - Actual study data
  - Who were the patients?
  - What was the chloroquine treatment?
  - What was the control treatment?
  - ***What were the results?***

Gao J., et al.

doi: 10.5582/bst.2020.01047.

- We have to see the actual studies and the data to determine if this is true.
- 7 references cited
  - None pertain to completed clinical studies of chloroquine in COVID-19

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Wang, M, et. al. Cell Research volume 30, pages269–271(2020)
doi: 10.1038/s41422–020–0282–0

Wang, M, et al

doi:
10.1038/s41422–020–0282–0

- Cells in a “petri dish”
- Infected with SARS-CoV-2
- Tested the effects of 7 different anti-viral medications
- 2 drugs “potently blocked virus infection at low concentration”
  - Remdesivir (next week)
  - Chloroquine

In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Yao, X, et. Al. Clinical Infectious Diseases (2020) doi: 10.1093/cid/ciaa237

Yao, X., et al

doi: 10.1093/cid/ciaa237

- Cells in a “petri dish”
- Infected with SARS-CoV-2
- Tested both drugs on the infected cells
- Both drugs prevented the virus from reproducing
  - Hydroxychloroquine was more potent
- Hydroxychloroquine also prevented cells from getting infected
- Used computer model to calculate the effective dose in humans would be non-toxic

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Gautret, P., et al. International Journal of Antimicrobial Agents (2020 pre-print)

doi: 10.1016/j.ijantimicag.2020.105949

Gautret, P et. al.

doi : 10.1016/j.ijantimicag.2020.105949

- Reporting preliminary results of ongoing study
- A lot of flaws with this paper
- Unable to draw any conclusions about whether the treatment is helpful or harmful

Gautret, P et. al. doi : 10.1016/j.ijantimicag.2020.105949

- *Non-randomized* to compare hydroxychloroquine to standard care
- Needed 48 patients to be statistically significant (RESULTS NOT DUE TO CHANCE)
- Enrolled *42 patients – not statistically significant*
  - 26 hydroxychloroquine
  - 16 control
- *6 patients (23%) in hydroxychloroquine group “Lost to follow up”*
  - 20 hydroxychloroquine
  - 16 control

Gautret, P et. al. doi : 10.1016/j.ijantimicag.2020.105949

Hydroxychloroquine 26 patients

- 6 “lost to follow up”
- 3 were admitted to ICU
- 1 died
- 1 left hospital after 3 days
- 1 quit taking medicine because of side effects
- *These patients were not included in the results but should have been – this is a huge flaw in the study*

Control – 16 patients

- All patients finished the study
- None were admitted to ICU
- None died.

Gautret, P et. al. doi : 10.1016/j.ijantimicag.2020.105949

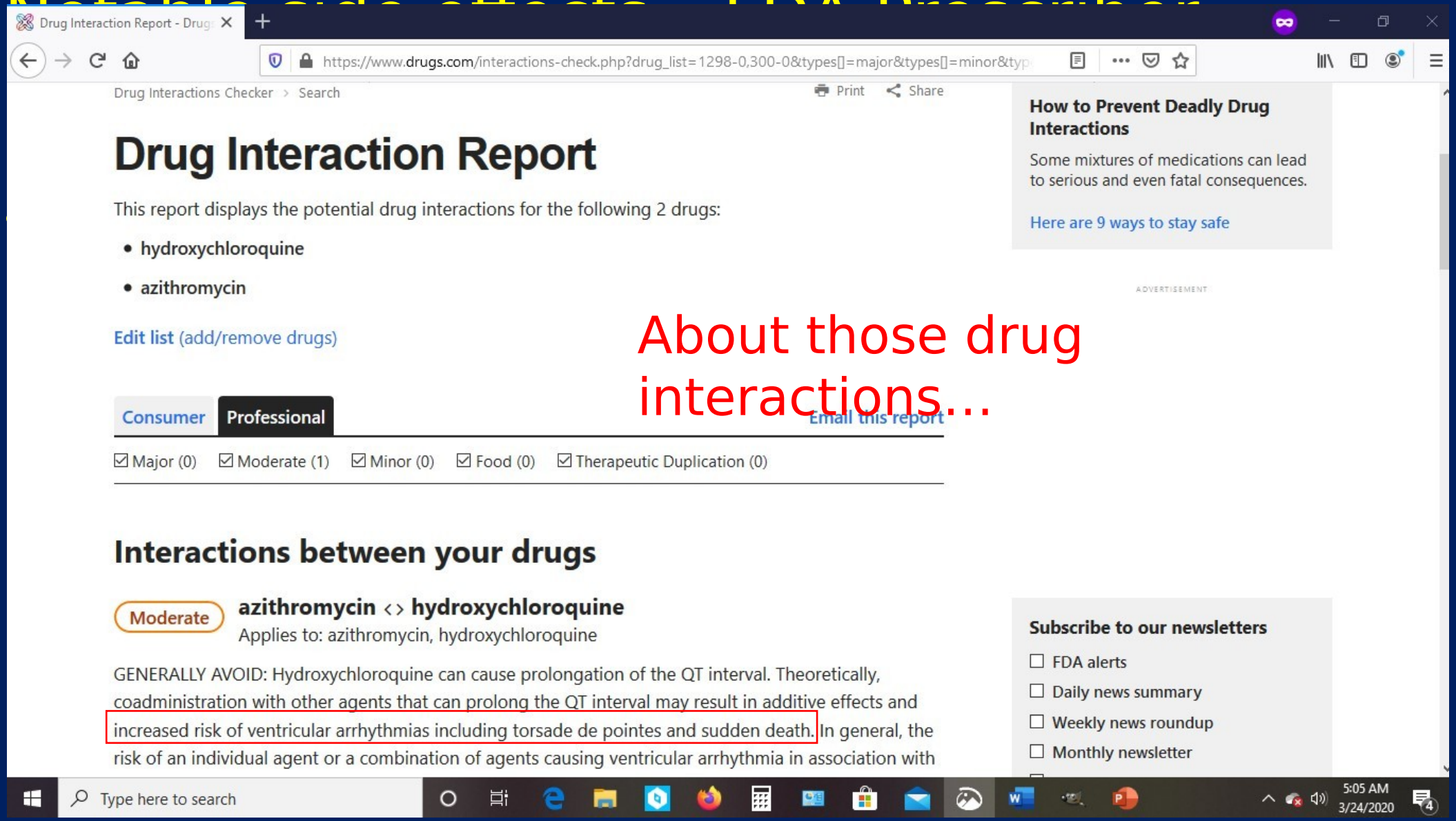
- Daily nasal swabs on every patient
- Control group – 16 patients
  - Day 6 12% negative
- Hydroxychloroquine group – 14 patients
  - Day 6 57% negative
- Hydroxychloroquine + azithromycin group – 6 patients
  - Day 6 100% negative
- *Results of these 6 were evaluated as a separate group.*
  - *It's ok to do this, but you need to define this group before you start*

Gautret, P et. al. doi : 10.1016/j.ijantimicag.2020.105949

- *Cannot conclude whether this treatment is helpful or harmful – only that it is worth it to do a larger study.*
- *Nothing in this study relates to using these drugs as prevention*

- *Now…*

Notable side effects - FDA Prescriber

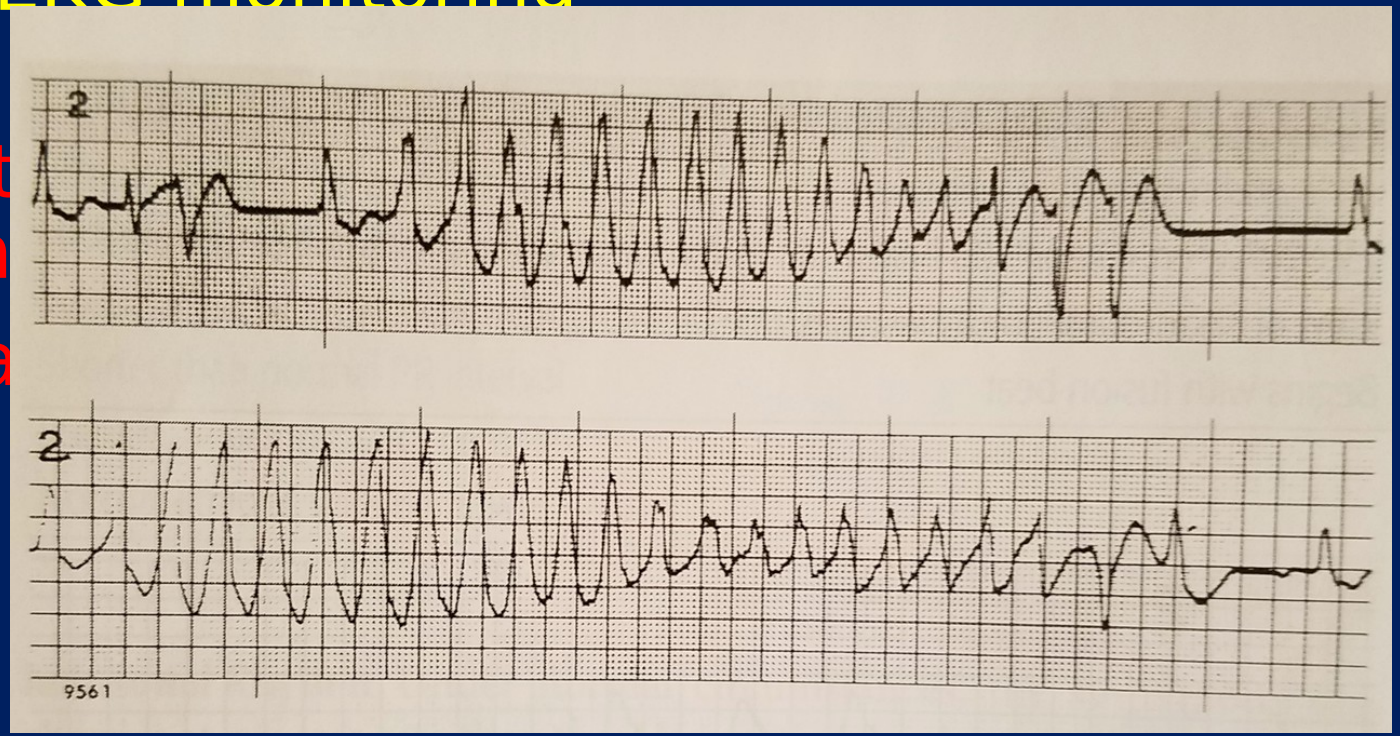


About those drug interactions…

Gautret, P et. al. doi : 10.1016/j.ijantimicag.2020.105949

- Because of this risk, all 6 patients getting both drugs had continuous EKG monitoring
- 1 in 2500 people have
  gene that
  m
- Need to be sure it is sa

  these drugs
  as an outpatient



Tintinalli, (ed.) Emergency Medicine: A Comprehensive Study Guide, 7th Ed. (2011) McGraw-Hill

Of Chloroquine and COVID-19

Touret, F. and de Lamballerie, X , Antiviral Research 177 (2020)
doi: 10.1016/j.antiviral.2020.104672

Touret and de Lamballerie

doi:10.1016/j.antiviral.2020.104672

- Review of research of Chloroquine and hydroxychloroquine on other viruses
- Effective in the lab (petri dish)
  - SARS
  - Chikungunya virus
- Effective in mice
  - Human coronavirus
  - Zika
  - Influenza A H5N1 (bird flu)
  - Ebola

Touret and de Lamballerie

doi:10.1016/j.antiviral.2020.104672

- Review of research of chloroquine and hydroxychloroquine on other viruses
- Harmful in non-human primates
  - Chikungunya

Touret and de Lamballerie

doi: 10.1016/j.antiviral.2020.104672

- Review of research of Chloroquine and hydroxychloroquine on other viruses
- Not effective in humans
  - Influenza prevention
  - Dengue
- Inconclusive in humans
  - HIV
  - Hepatitis C
- Not effective, and possibly harmful in humans
  - Chikungunya

Touret and de Lamballerie

doi: 10.1016/j.antiviral.2020.104672

“Altogether, the assessment of previous trials indicates that, to date, no acute virus infection has been successfully treated by chloroquine in humans.”

So, what’s the bottom line? Should I take them or not?

I can only speak for myself

- I would not prescribe them for myself
- I would not prescribe them for my family
- There is *no proof* of benefit
- All drugs have side effects
- Even if the side effects are minimal, why go through it if there is no benefit?
- Even if the chance of sudden death is 1 in 10 million, right now the proof of benefit is 0 in 10 million
- Until I see better studies, this is where I stand

Where to go from here?

- Robust clinical studies
- 23 clinical trials registered in Chinese Clinical Trials Registry
- Clinical trials underway in New York, Spain, and France
- Clinical trials planned in Germany, Norway, Korea, Mexico, England, USA
- https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=&cntry=&state=&city=&dist=&Search=Search
- http://www.chictr.org.cn/searchprojen.aspx
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19

Conclusion

- Chloroquine and hydroxychloroquine are effective at blocking SARS-CoV-2 in a lab setting
- The few published reports of successful treatment in humans are *deeply flawed* and cannot be used as evidence that these drugs will be beneficial
- Though extremely rare, they can have serious side effects and be fatal in children who accidentally ingest even small amounts
- More studies are needed and are underway!

Thank you!

- Amanda Lewis
- Janet Phillips
- Greg Shores
- Brittney VanDerWerff

These presentations don’t get out to you without their help!

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