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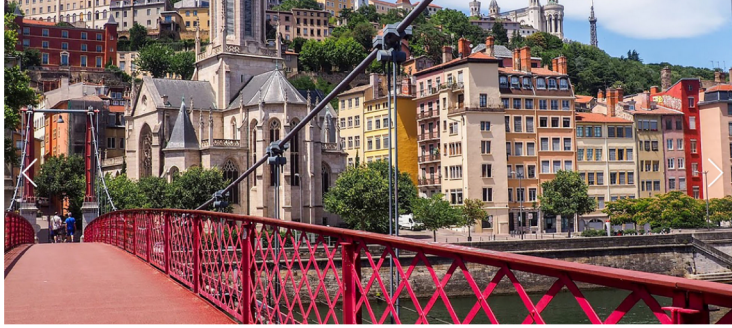
ACTUALITÉS EN RÉANIMATION



Toxicology:
What to remember from 2020-2021?

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

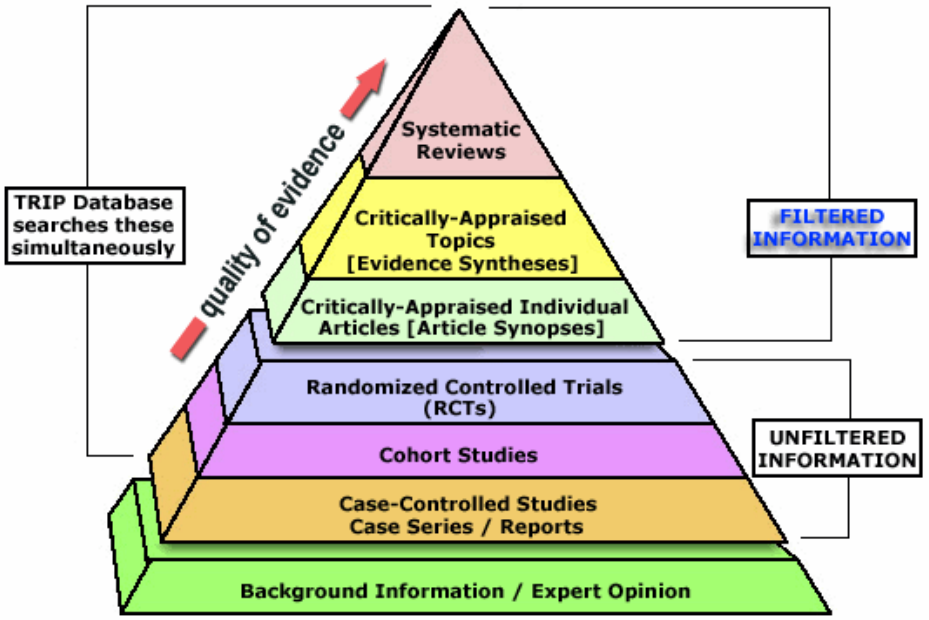
Université de Paris

No conflict of interest

What types of paper in clinical toxicology?

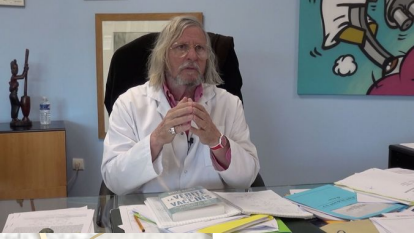
Medical toxicology literature

- Poison Centre Research
- Clinical Observational Research
- Case report
- Basic Research
- Review
- Metanalysis
- Expert Opinion

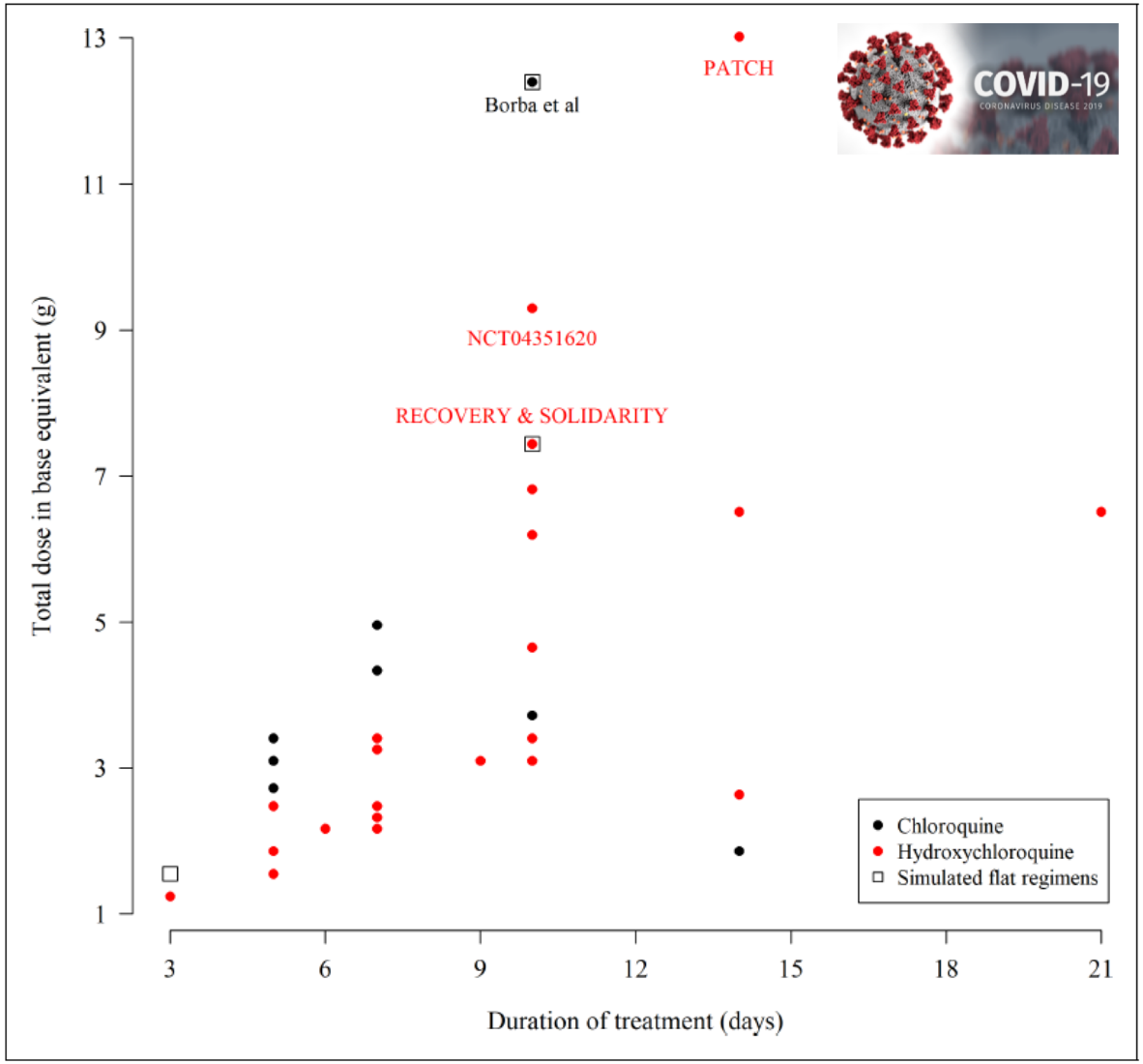


Critical points

- Rare randomized clinical trial → number of patients / ethical issues
- Case reports = fundamental in clinical toxicology
  - increasingly difficult to find journal accepting them



Total dose and duration of 55 (hydroxy)chloroquine trials in COVID-19



THE LANCET

Published May, 2020
Retracted June, 2020

Surgisphere

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation m[illegible]ide, are b[illegible] widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although [illegible]nerally [illegible]e whe[illegible] used for approved indications such as autoimmune disease or malaria, the safety and bene[illegible]f th[illegible]treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine [illegible]oquine with[illegible]thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hosp[illegible]s in s[illegible]ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory [illegible]g for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn[illegible]f included in [illegible]f four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor[illegible]ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed [illegible] control gr[illegible]. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis o[illegible]ile they w[illegible]on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc[illegible]of int[illegible]st were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias [illegible]tained o[illegible]ed ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women[illegible]OVID-19 were hospitalised during the study period and met the inclusion criteria. Of the[illegible] patie[illegible] were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with[illegible]macr[illegible]e, 3016[illegible]eived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and [illegible]4 pati[illegible]s in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple [illegible] fou[illegible]ctors ([illegible] sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac[illegible], diabetes[illegible]derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), w[illegible]mpared wi[illegible]ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95%[illegible]·2[illegible]457), hydr[illegible]ychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, [illegible]318–1·531), [illegible]chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated [illegible]n an increased [illegible]f in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6[illegible]; 2·36[illegible]·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; [illegible]1, 7[illegible]0–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate[illegible]an incr[illegible]ed risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretati[illegible] We v[illegible]e unabl[illegible]nfirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macr[illegible]on in[illegible]spital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospita[illegible]vi[illegible]reased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Funding Willia[illegible]vey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

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[illegible]22, 2020
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See Online/Comment
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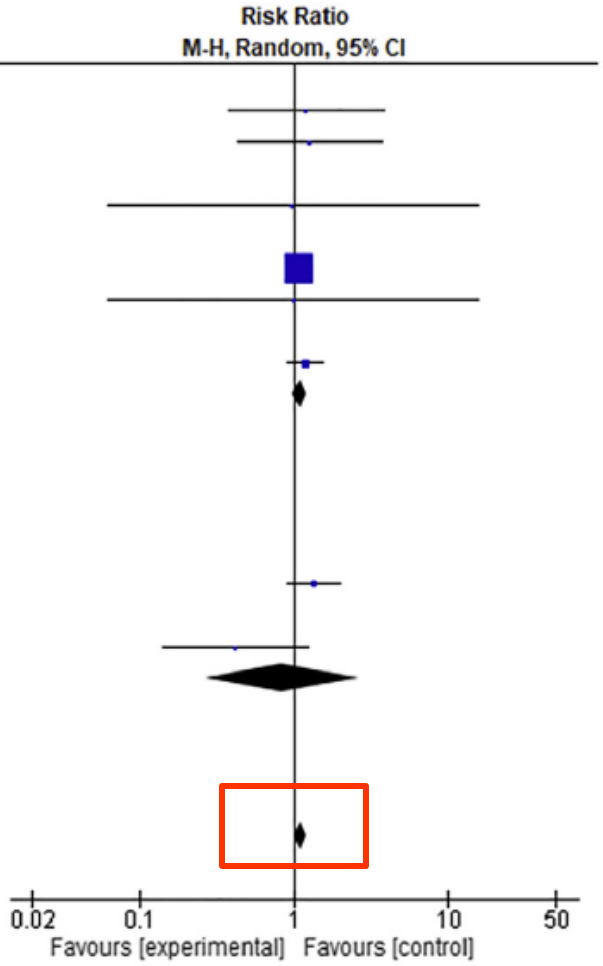
RETRACTED

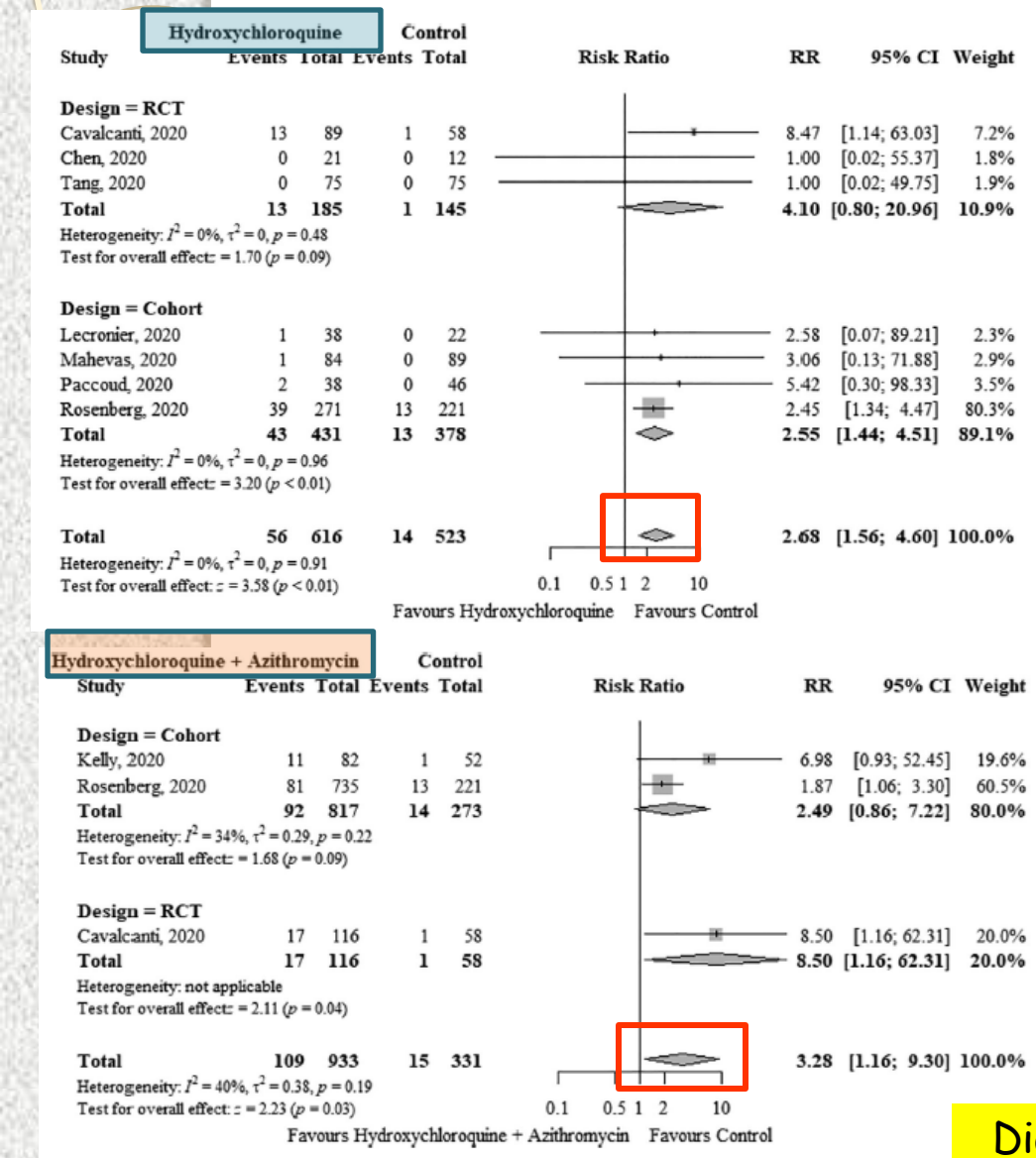
Comparison of mortality among COVID-19 patients receiving hydroxychloroquine *vs* standard of care

Study or Subgroup	Hydroxychloroquine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Randomized studies						
Abd-Elsalam S 2020	6	97	5	97	0.6%	1.20 [0.38, 3.80]
Cavalcanti AB 2020	7	159	6	173	0.7%	1.27 [0.44, 3.70]
Chen Jun 2020	0	15	0	15		Not estimable
Lofgren SM 2020	1	576	1	563	0.1%	0.98 [0.06, 15.59]
Mitjà O 2020	0	136	0	157		Not estimable
RECOVERY Collabortaive Group 2020	421	1561	790	3155	81.0%	1.08 [0.97, 1.19]
Skipper CP 2020	1	212	1	211	0.1%	1.00 [0.06, 15.81]
Tang W 2020	0	75	0	75		Not estimable
WHO Solidarity trial	104	947	84	906	11.2%	1.18 [0.90, 1.56]
Subtotal (95% CI)		3778		5352	93.8%	**1.09 [0.99, 1.20]**
Total events	540		887			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 5 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
1.1.2 Non-Randomized studies						
Grimaldi D 2020	80	220	23	85	5.5%	1.34 [0.91, 1.99]
Huang M 2020	0	197	0	176		Not estimable
Karolyi M 2020	3	20	32	89	0.7%	0.42 [0.14, 1.23]
Subtotal (95% CI)		437		350	6.2%	**0.84 [0.27, 2.62]**
Total events	83		55			
Heterogeneity: Tau² = 0.53; Chi² = 4.10, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		4215		5702	100.0%	**1.10 [1.00, 1.20]**
Total events	623		942			
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 7 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



Kumar J. *J Infect Chemother* 2021

QTc prolongation in COVID-19 patients treated with hydroxychloroquine ± azithromycin: A meta-analysis



➔ Relatively high prevalence of QTc prolongation

➔ Very low prevalence of arrhythmic events, probably due to underreporting

➔ Other causes such as COVID-19-reated myocarditis

Diaz-Arocutipa C. *Pharmacoepidemiol* 2021

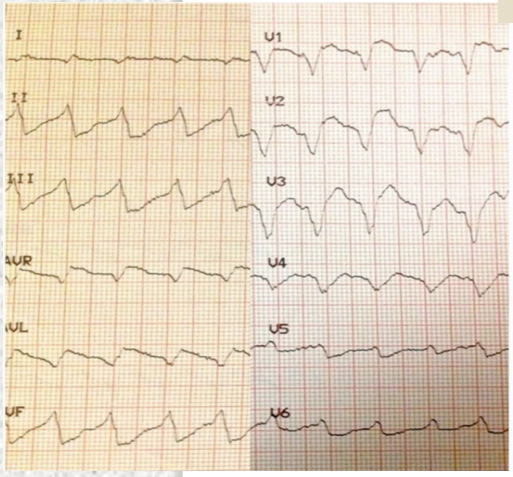
Hydroxychloroquine/chloroquine poisonings
Clinical features

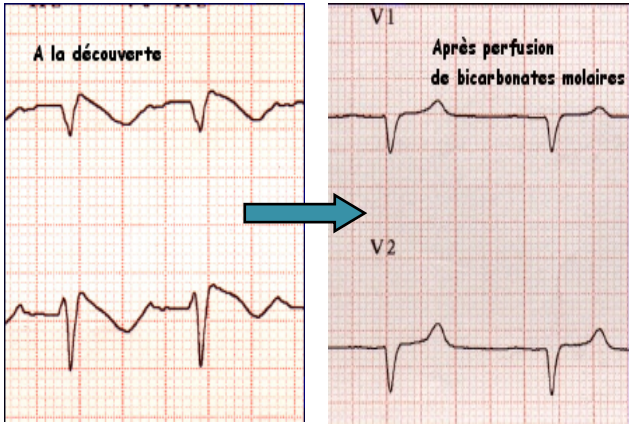
- **Cardiovascular syndrome:**

  ECG : QRS enlargement, QT prolongation, AV blocks (rare)

  Circulation : Cardiogenic and vasoplegic shock
- **Metabolic syndrome** : Hypokalemia, lactic acidosis
- **Neurological syndrome** : Convulsive coma
- **Respiratory syndrome** : Delayed ARDS with alveolar hemorrhage

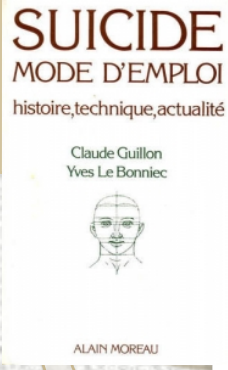
On admission | Sodium bicarbonate





QRS duration (msec)	Seizure risk	Ventricular dysrhythmia risk
< 100	mild	mild
100 - 160	moderate	mild
> 160	elevated	elevated

Boehnert MT. *NEJM* 1985



Chloroquine poisoning: prognosis assessment and management

	Supposed ingested dose		Systolic BP		QRS duration
Severe	≥ 4 g	or	< 100 mmHg	or	> 0.10 s
Mild	< 2 g	and	≥ 100 mmHg	and	≤ 0.10 s

Clemessy JL, et al. Crit Care Med 1996

Severe poisoning :

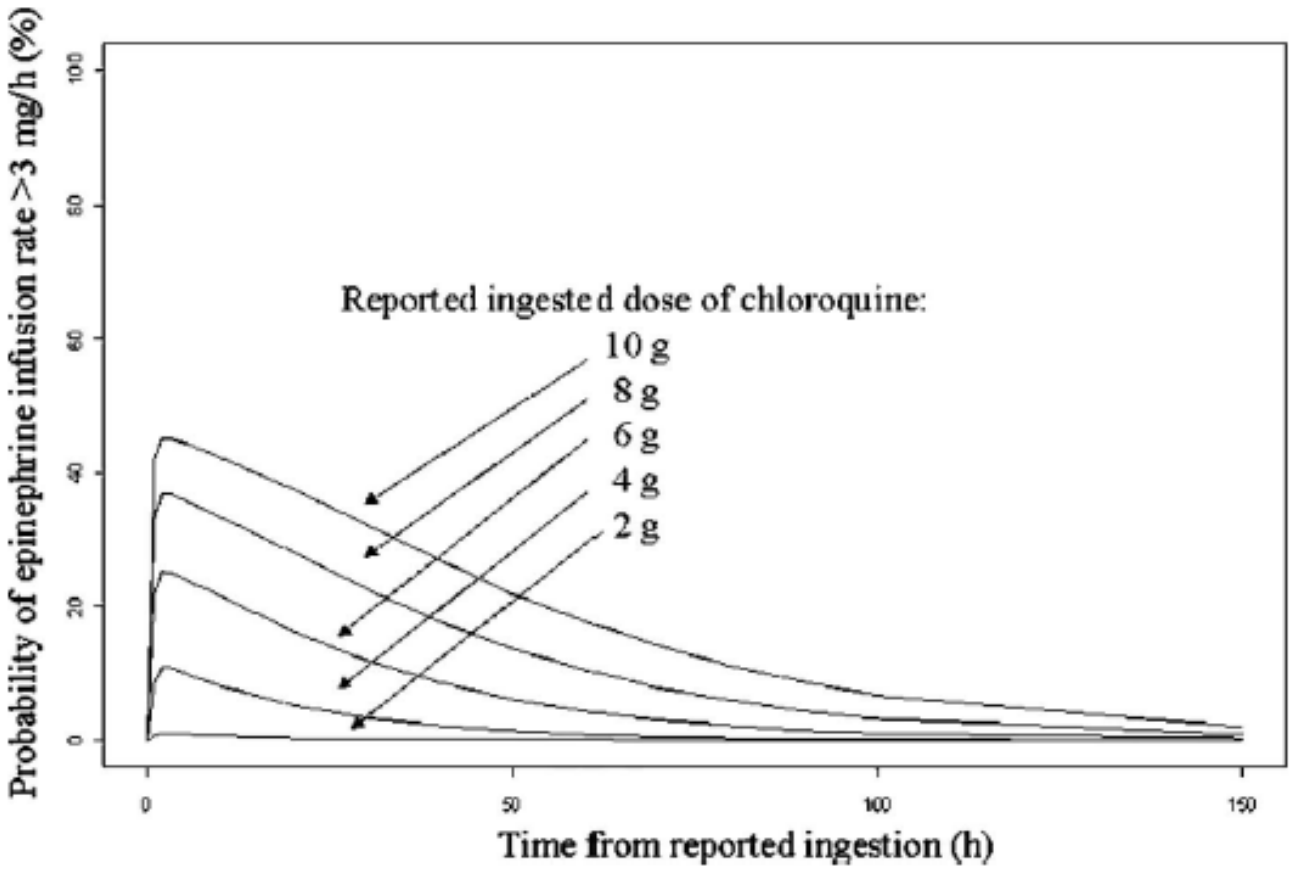
- Intubation and mechanical ventilation
- Epinephrine 0.25µg/kg/min with ↗0.25µg/kg/min steps to obtain SBP ≥100 mmHg
- Diazepam 2 mg/kg in 30 min followed with 2-4 mg/kg/24h
- 8.4% sodium bicarbonate 250 mL (+ 2g KCl), up to 3 times

Riou B. *N Engl J Med* 1988

- va-ECMO

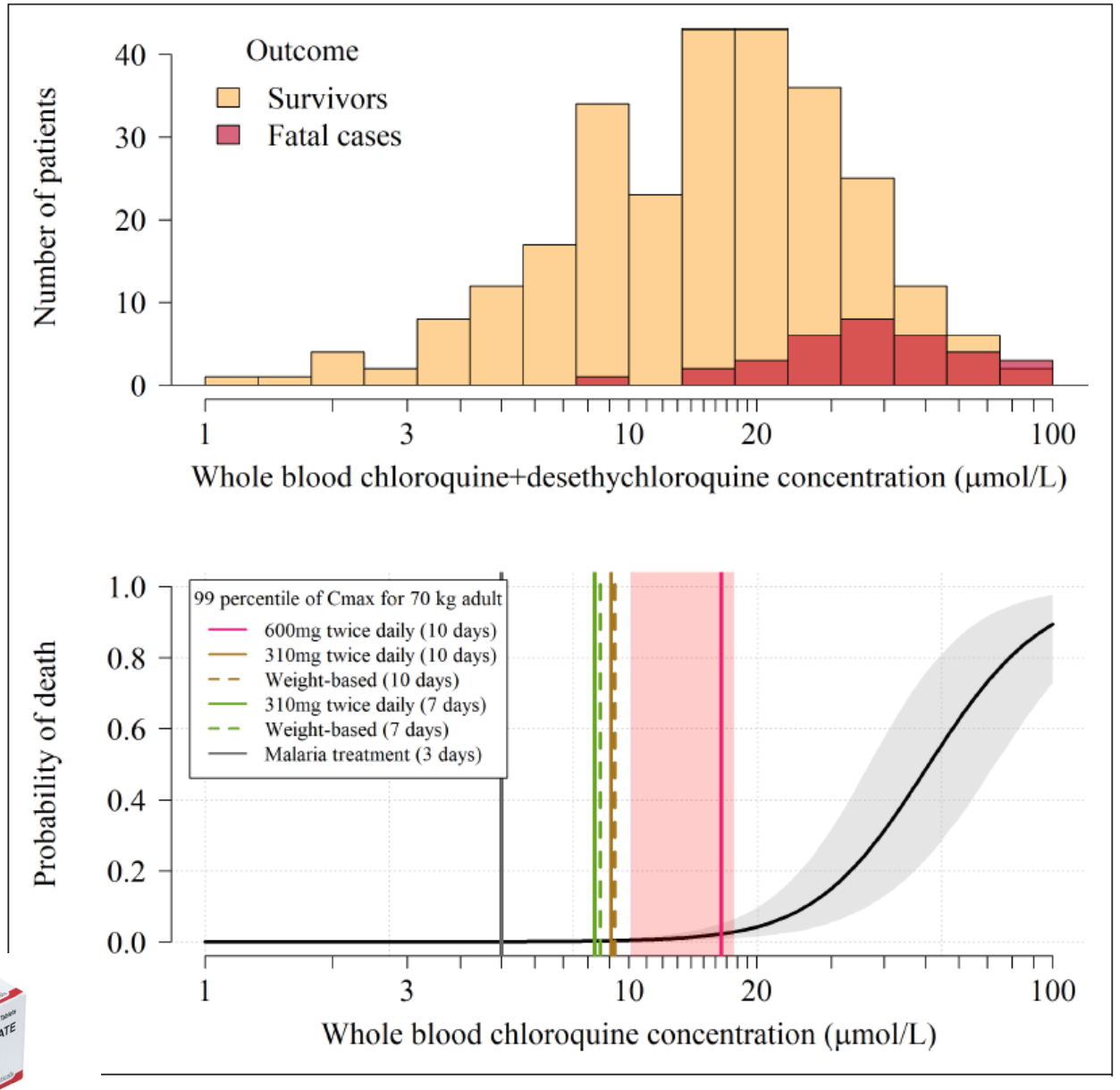
The prognostic value of the ingested dose

Simulated probability over time for having an epinephrine infusion rate >3 mg/h



Mégarbane B. *Clin Tox* 2011

PK-PD model of chloroquine-induced mortality



Watson JA. *Elife* 2020

Toxicity resulting from colchicine used to treat COVID-19: a new challenge for clinical toxicologists

	Acute poisoning	Adverse effects
Causes	• Drug overdose • Ingestion of colchicine-containing plants	• Renal impairment • Drug-drug interactions
Clinical course	• Phase I: Vomiting, Diarrhea, Hypovolemia, Leukocytosis • Phase II: Cardiovascular shock, Liver failure, Renal failure, Myelosuppression, Multi-organ failure • Phase III: Rebound leukocytosis Alopecia	• The three phases are lacking • Gastrointestinal manifestations (common) • leucopenia with risk of bacterial infection (rare) • thrombocytopenia (rare)
Treatment	• Gastrointestinal decontamination • Supportive (fluids, vasopressors, antibiotics, mechanical ventilation, hemodialysis, transfusions, colonial grow factors)	• Drug cessation • Dose adjustment
Colchicine plasma concentration	• Possible prognostic value if related with time from ingestion	• monitoring tool for dose adjustment in case of renal impairment or drug-drug interactions

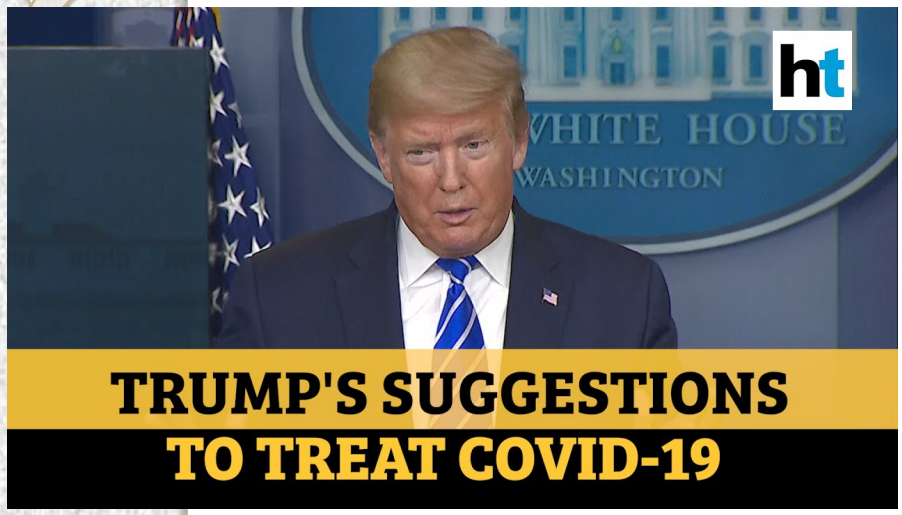
Cumulative colchicine doses ranging from 8 to 22mg administered from 5 to 30 days

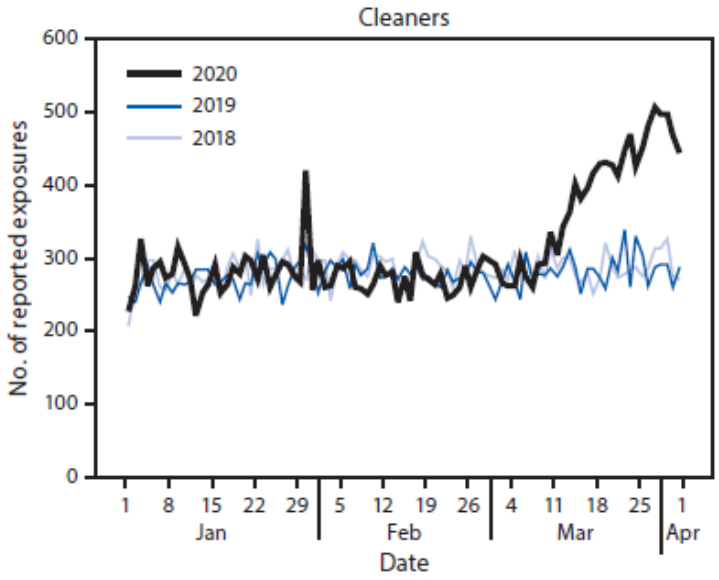
Toxicity resulting from colchicine used to treat COVID-19: Drug-drug interactions

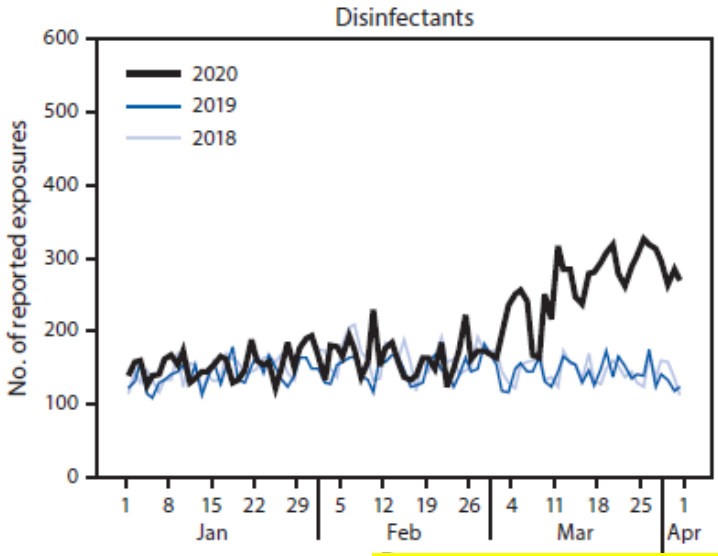
Anti-COVID-19 drugs	Potential drug-drug interaction with colchicine*
Anakinra (anti- Interleukin-1 receptor monoclonal antibody)	None
Azithromycin (and other macrolides)	Increase in plasma and intracellular colchicine concentrations resulting from the inhibition of its P-glycoprotein-mediated efflux transport at the intestinal barrier (increased absorption) and in the liver (reduced metabolism)
Baloxavir	None
Bamlanivimab (anti-Spike protein monoclonal antibody)	None
Baricitinib (anti-Janus kinase-1 and −2 monoclonal antibody)	None
Casirivimab/Imdevimab (anti-Spike protein monoclonal antibodies)	None
Chloroquine/Hydroxychloroquine	None
Dimethyl fumarate	None
Direct anti-Xa inhibitors (Rivaroxaban, Apixaban)	None
Furosemide	None
Heparin (unfractionated and low molecular weight)	None
Interferons (beta-1A and alpha-2B)	None
Ivermectine	None
Lopinavir/Ritonavir	Increase in plasma and intracellular colchicine concentrations resulting from the inhibition of its cytochrome P450 3A4-mediated liver metabolism
Remdesivir	None
Ribavarin	None
Ruxolitinib (anti-Janus kinase-1 and −2 monoclonal antibody)	None
Salicylates	None
Sarilumab (anti- Interleukin-6 receptor monoclonal antibody)	None
Sofosbuvir/Daclatasvir	None
Steroids (Dexamethasone, Methylprednisolone, Prednisone, Prednisolone)	Decrease in plasma and intracellular colchicine concentrations resulting from the induction of its cytochrome P450 3A4-mediated liver metabolism
Tocilizumab (anti-Interleukin-6 receptor monoclonal antibody)	None

Schicchi A. *Clin Tox* 2021

Non-authorized therapies:
Household cleaners and disinfectants

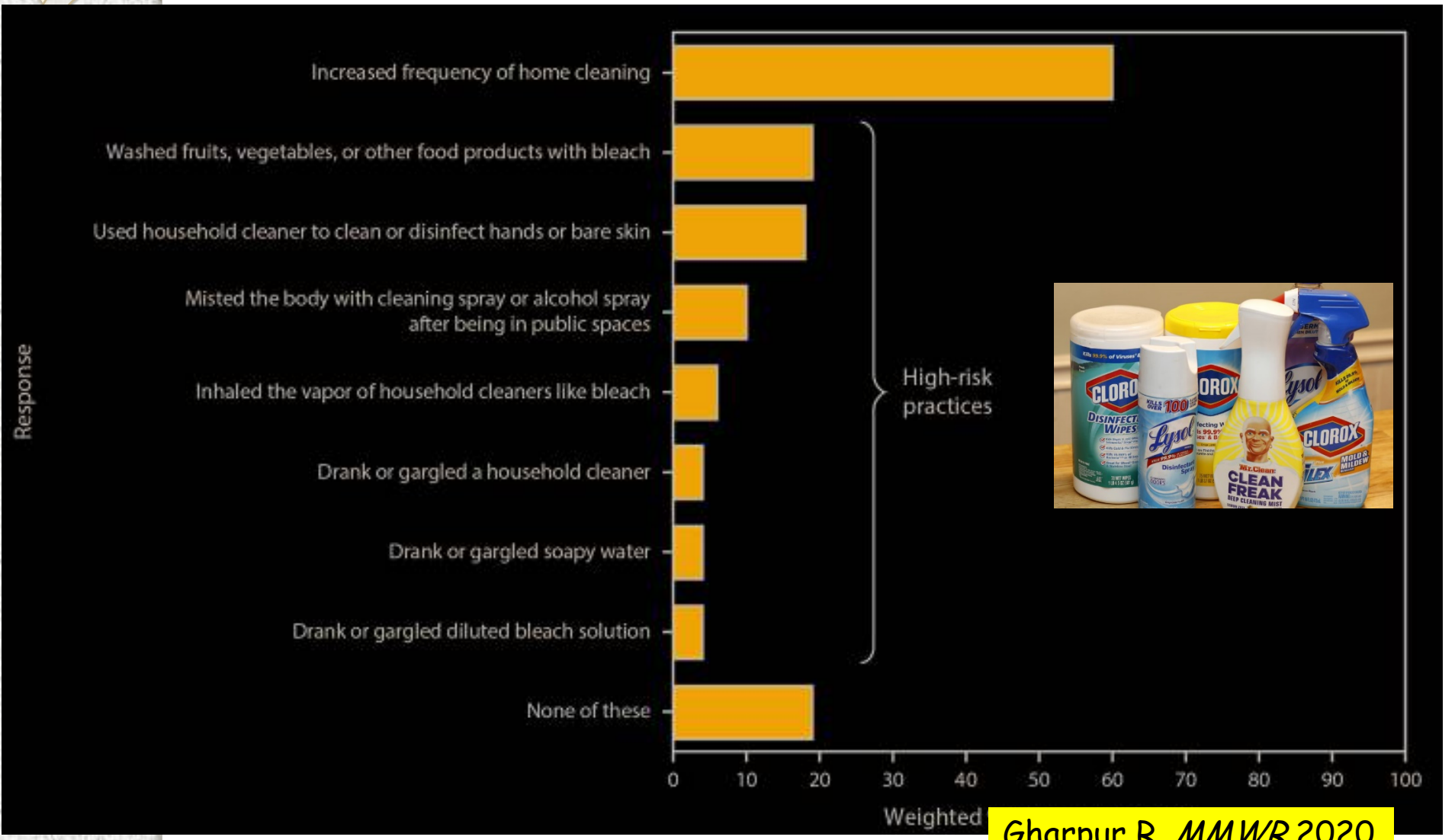






Chang A. *MMWR* 2020

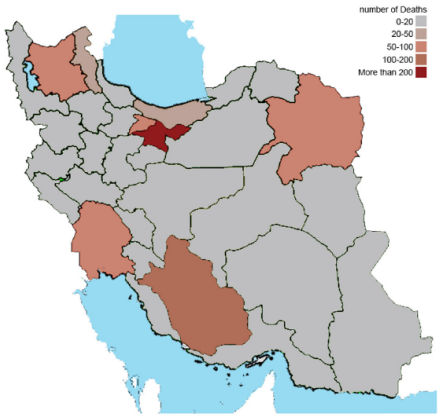
Practices Regarding Safe Household Cleaning and Disinfection for COVID-19 Prevention, in the US, 2020



Gharpur R. *MMWR* 2020

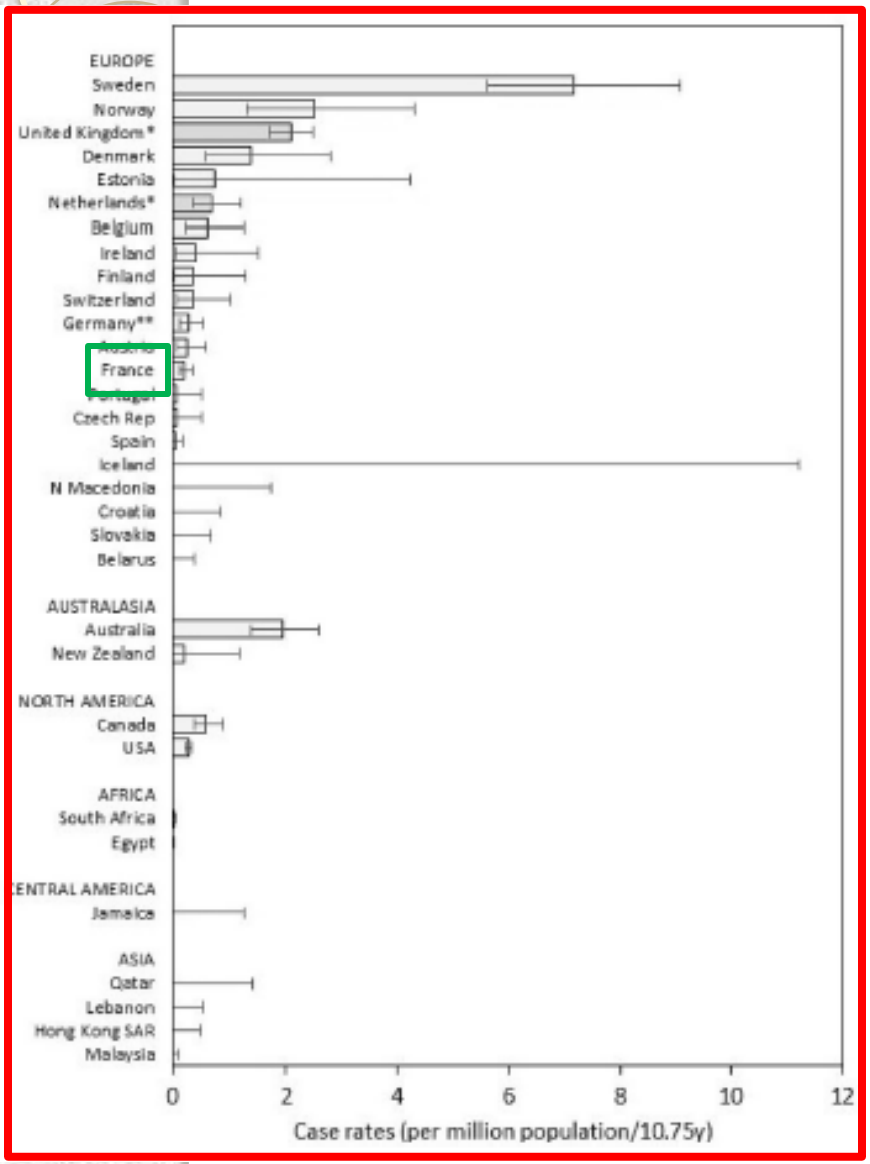
Double trouble: methanol outbreak in the wake of the COVID-19 pandemic in Iran

Province	Poisoning cases: hospital admissions (source: MOH)	Methanol deaths*	
		In hospital (source: MOH)	Total registered (source: LMO)
Tehran	1177	87	205
Khuzestan	1079	93	88
Fars	812	99	139
Razavi Khorasan	581	67	78
East Azerbaijan	483	50	75
Alborz	248	43	52
Ardebil	223	22	31
Isfahan	207	6	19
Kerman	139	0	2
Kermanshah	132	2	2
Mazandaran	100	10	28
Yazd	96	12	10
Markazi	87	4	4
Kurdestan	79	0	9
The other provinces	433	39	58
Total	**5876**	**534**	**800**



Hassanian-Moghaddam H. *Crit Care* 2021

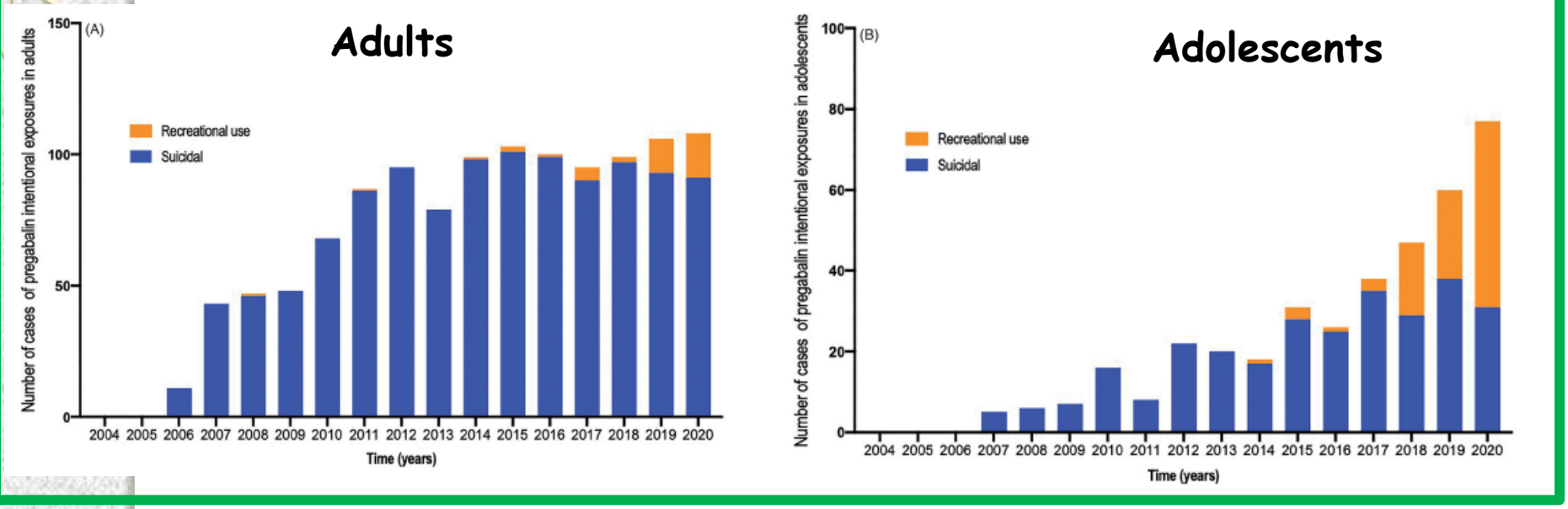
International trends in systemic exposures to 2,4-dinitrophenol reported to PCCs



- Toxic industrial chemical to ↓weight
- Uncoupling oxidative phosphorylation
- 38 countries, 456 PCC cases
- Annual N: ↑4 in 2010 to 71 in 2019
- Austral, Eur, N Am > Asia, Af, S Am
- Substantial differences between countries within the same continent
- Case fatality high: 11.9% [9.0-15.4]

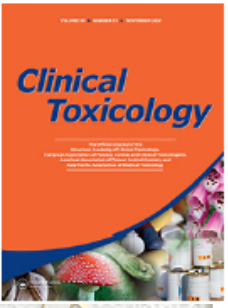
Gziut T. *Clin Tox*2021

Increase in pregabalin recreational use in adolescents in France



M/F ratio: 5.3/1; median age: 15 years (range: 11–17.8)
Homeless or living in migrant shelters (81%)
Two-third of exposures involved other toxicants
Asymptomatic (11%) or minor-to-moderate neurological symptoms (81%)
Severe cases: coma, generalized seizures requiring intubation

Dufayet L. *Clin Tox* 2021



Systematic review on the use of activated charcoal for GI decontamination following acute oral overdose

22,950 titles ➔ 296 human, 118 animal, and 145 in vitro studies

- Quality: Low or Very Low GRADE (83%)
- The higher GRADE studies reported on: acetaminophen, phenobarbital, carbamazepine, cardiac glycosides, ethanol, iron, salicylates, theophylline, tricyclic antidepressants, and valproate.

- Data on newer pharmaceuticals: quetiapine, olanzapine, citalopram, and Xa inhibitors

- No study on the optimal dosing for single/multiple-dose charcoal
- Time of administration: >1h (97%), >2h (36%), >12 h (4%)
  but in RCT : <1h (48%), <2h (36%)

Hoegberg L. *Clin Tox* 2021

Clinical utility of VA-ECMO in patients with drug-induced cardiogenic shock - The ELSO case registry (N=104)

55 Survivors (53%)

VA-ECMO duration: 68 h [48-113]

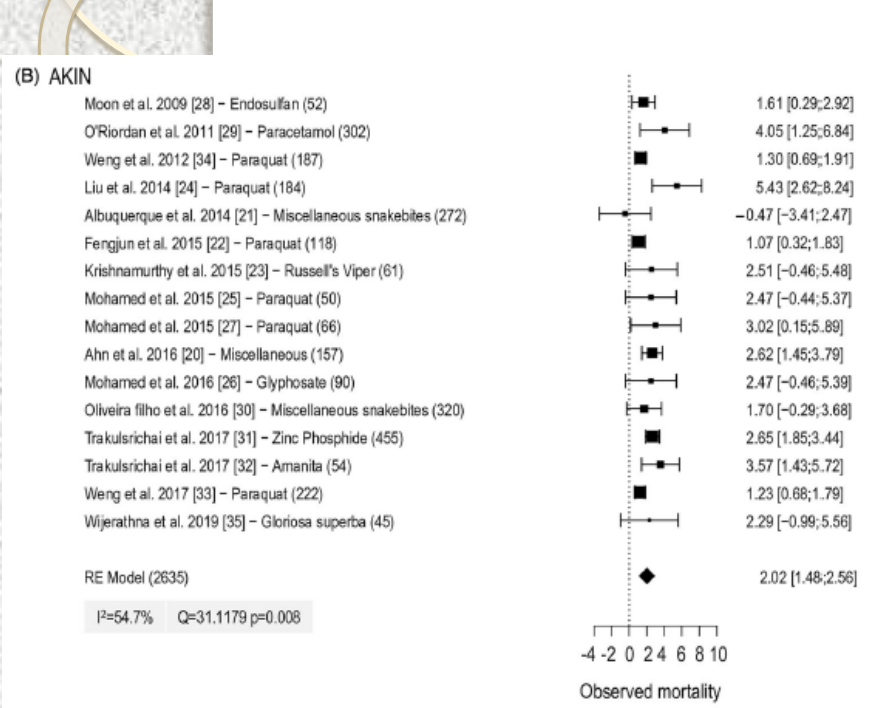
Significant improvement of hemodynamics (MAP, BP), acidosis (pH, HCO_3) and ventilatory parameters (PaO_2, SpO_2, and SvO_2)

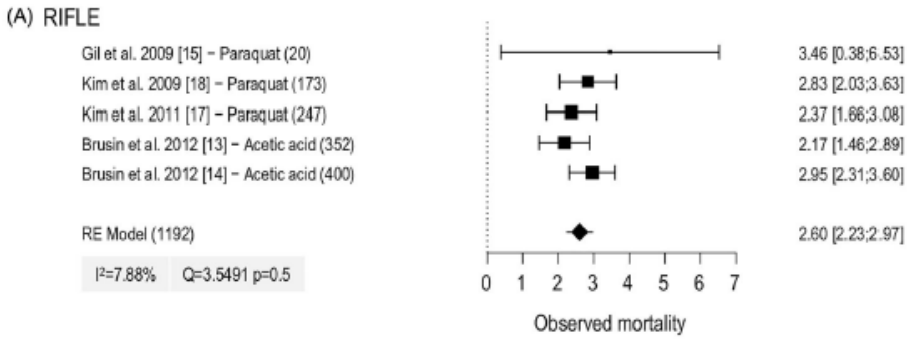
Univariate tests of association for in-hospital mortality

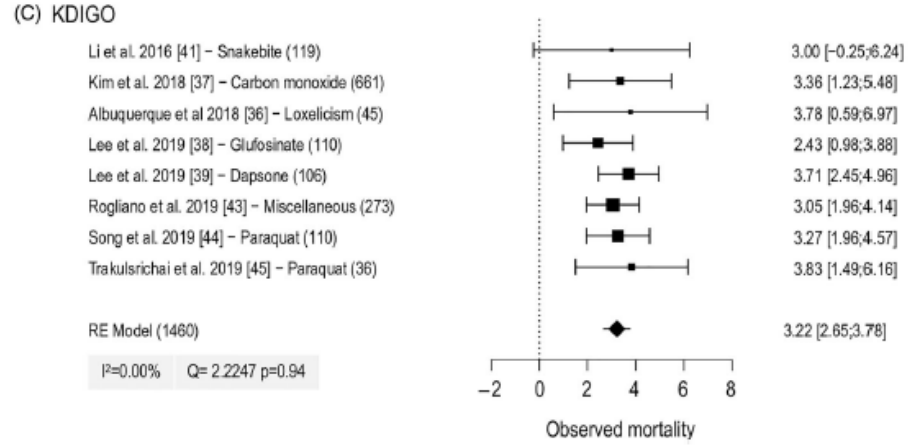
Variables	OR [95% CI]
Demographic	
Age	1.02 [0.99–1.05]
Male gender	1.96 [0.88–4.33]
Pre-ECMO variables	
CV agent vs. non-CV agent	0.64 [0.29–1.40]
pH at cannulation	0.38 [0.03–5.44]
HCO_3 at cannulation	1.01 [0.97–1.05]
MAP at cannulation	0.99 [0.96–1.02]
Pre-ECMO arrest	1.47 [0.64–3.34]
Intra-aortic balloon pump	13.72 [0.74–254.84]
Pacemaker insertion	3.01 [0.56–16.29]
Organ failures during ECMO	
Renal replacement therapy	0.57 [0.24–1.37]
Hyperbilirubinemia	3.92 [0.43–35.71]

Weiner L. *Clin Tox* 2020

Relationship between AKI and mortality in poisoning – a systematic review and metanalysis







All three consensus classifications were associated independently with increased mortality in poisoning but with disparity between studies.

Vodovar D. *Clin Tox* 2021

What is the exact place of elimination techniques in the management of poisonings?

EXTRIP recommendations

Recommendations from the EXTRIP workgroup on extracorporeal treatment for baclofen poisoning

In severe acute baclofen poisoning, we suggest against ECTR in addition to standard care, but rather support standard care alone (weak, very low quality).

In severe toxicity from therapeutic baclofen in kidney impairment, we suggest ECTR in addition to standard care, rather than standard care alone (weak, very low quality).

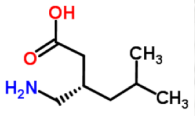
Indications: In patients presenting with toxicity from therapeutic baclofen in kidney impairment, we suggest ECTR in the presence of coma requiring mechanical ventilation (weak, very low quality).

Type of ECTR: We recommend intermittent hemodialysis, rather than any other type of ECTR (strong, very low quality).

Cessation of ECTR: We recommend stopping ECTR based on clinical improvement (strong, very low quality).

Ghannoum M. *Kidney Int* 2021

Extracorporeal Treatment for Gabapentin and Pregabalin Poisoning: Systematic Review and Recommendations From the EXTRIP Workgroup



In patients severely poisoned with gabapentinoids and normal kidney function, we suggest against ECTR in addition to standard care rather than standard care alone (weak, very low quality).

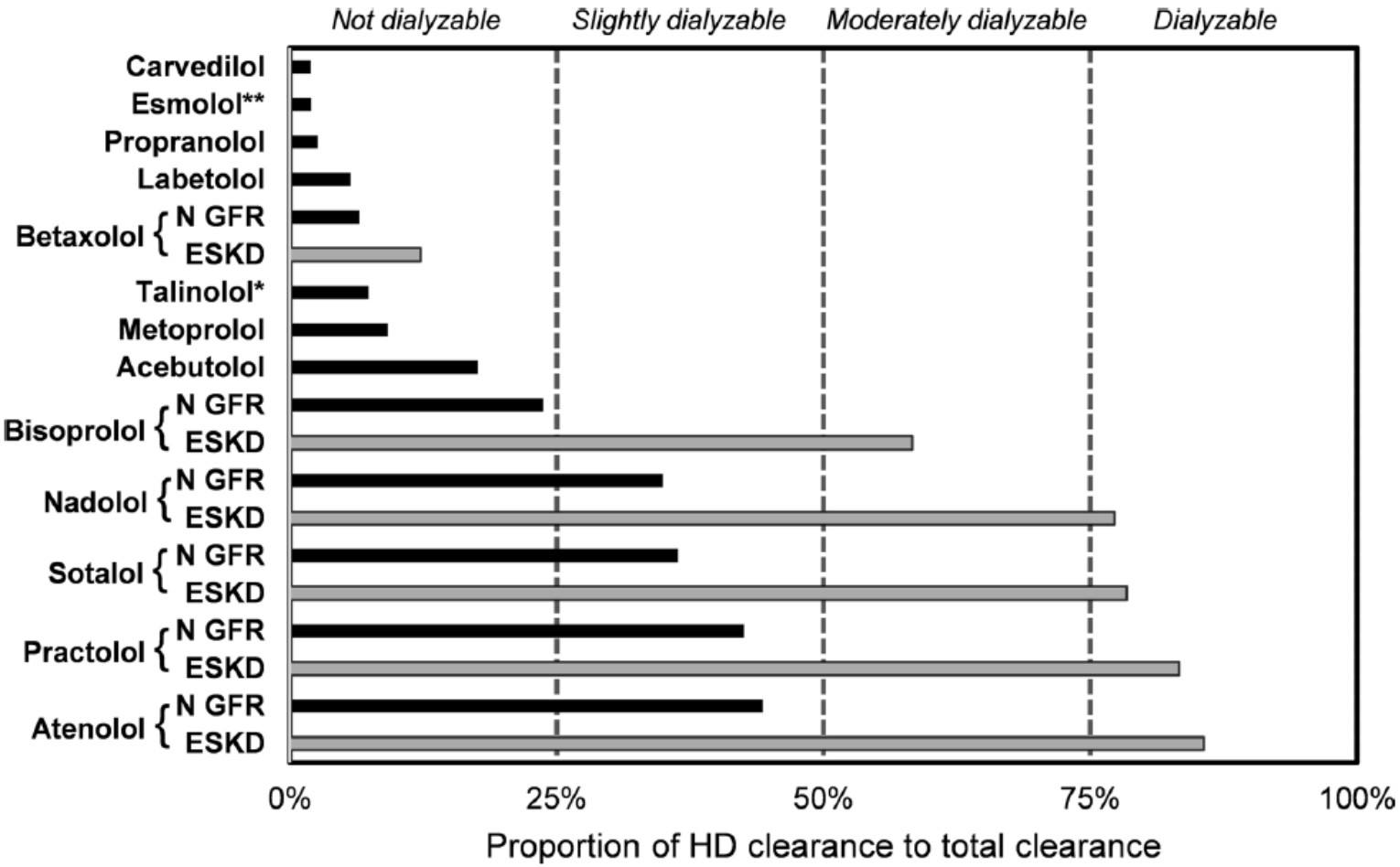
In patients severely poisoned with gabapentinoids and coexisting kidney impairment, we suggest ECTR in addition to standard care rather than standard care alone, especially in the presence of coma requiring mechanical ventilation (weak, very low quality).

Type of ECTR: we recommend intermittent hemodialysis rather than any other type of ECTR (strong, very low quality).

Cessation of ECTR: we recommend stopping ECTR based on clinical improvement (strong, very low quality).

Bouchard J. *AJKD* 2021

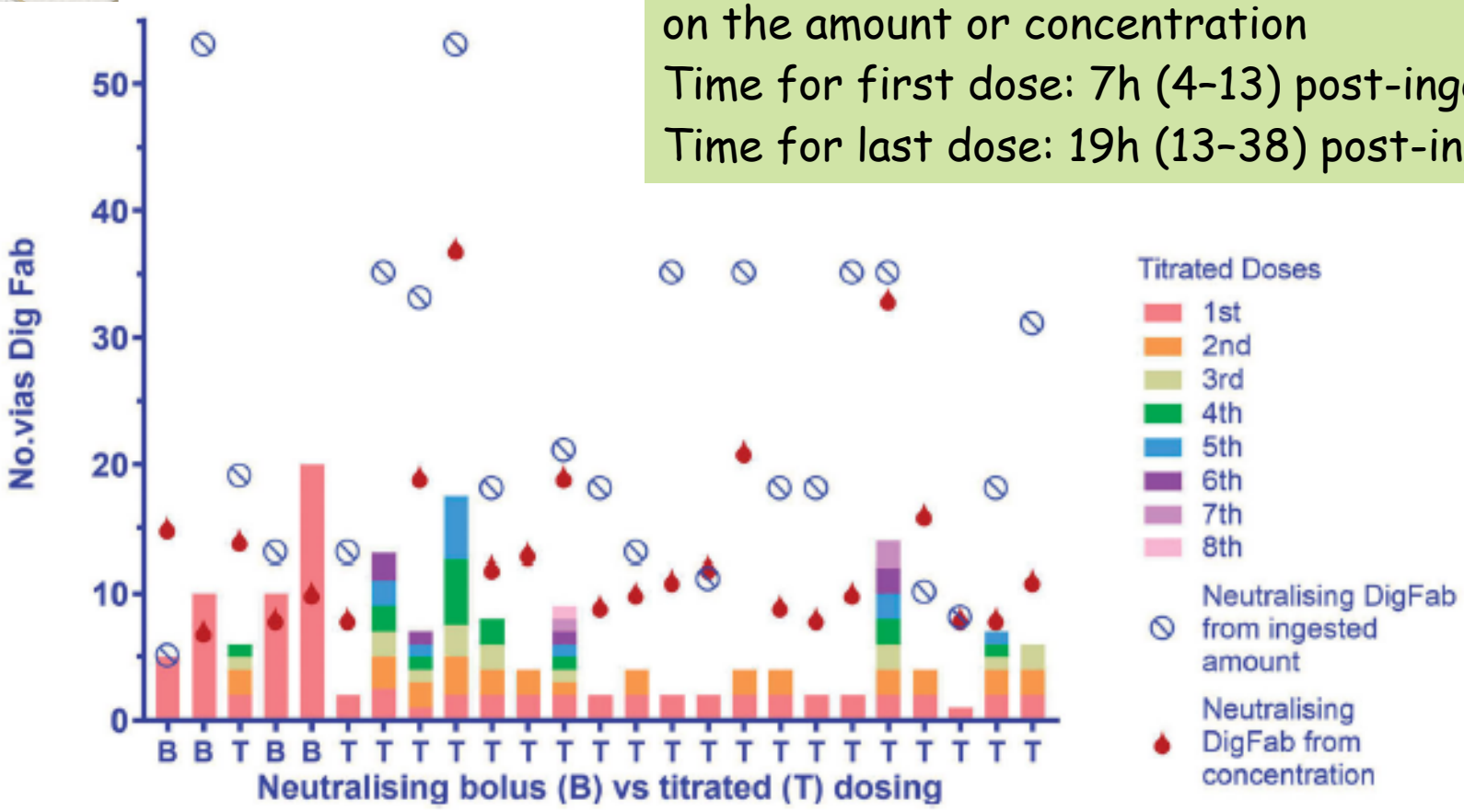
Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup



Bouchard J. *Crit Care* 2021

Clinical experience with titrating doses of digoxin antibodies in acute digoxin poisoning

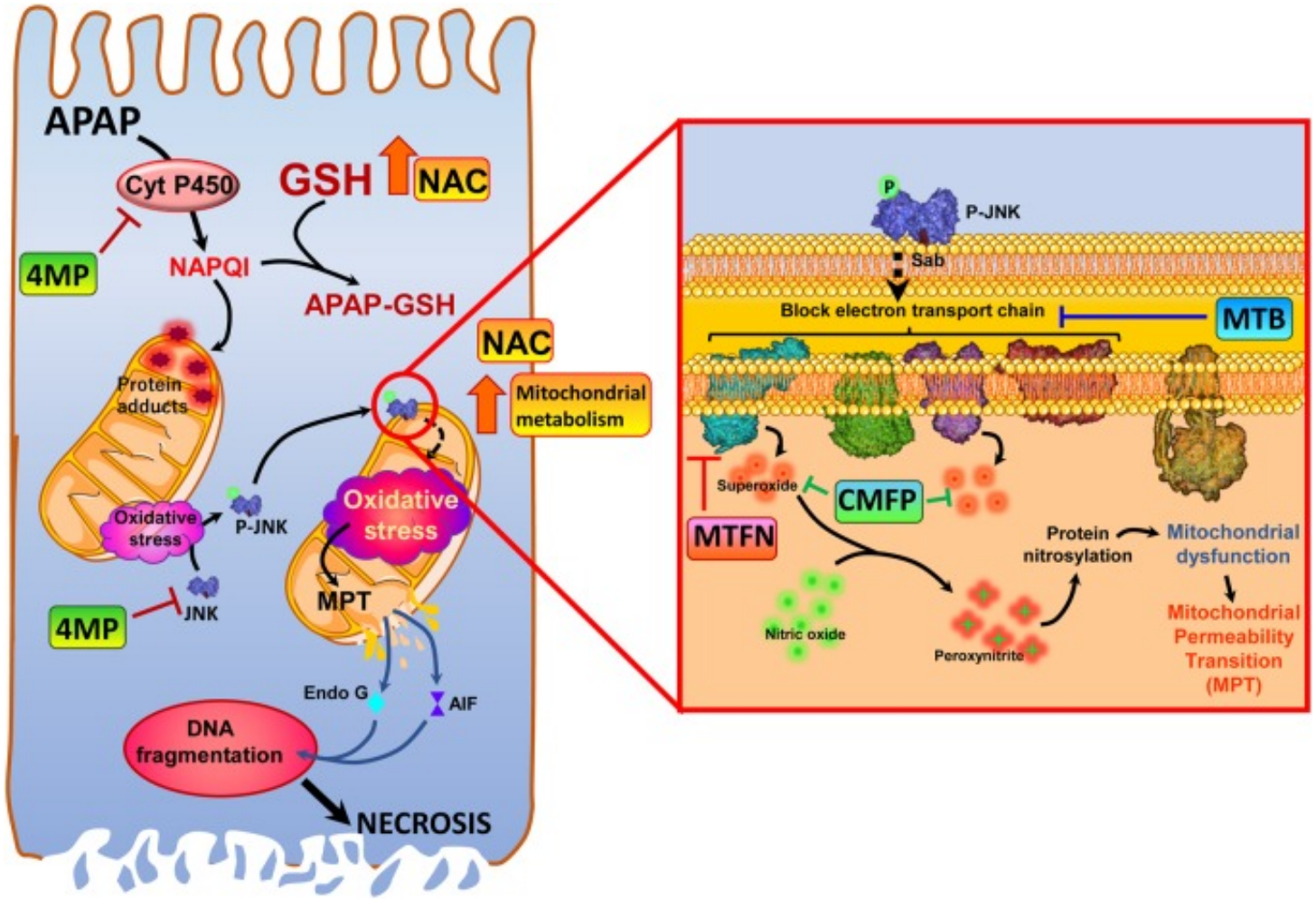
Initial dose: 2 vials - Total dose: 4 vials
Total dose = 25% and 35% doses given based on the amount or concentration
Time for first dose: 7h (4–13) post-ingestion
Time for last dose: 19h (13–38) post-ingestion



Chan BS. *Clin Tox* 2021

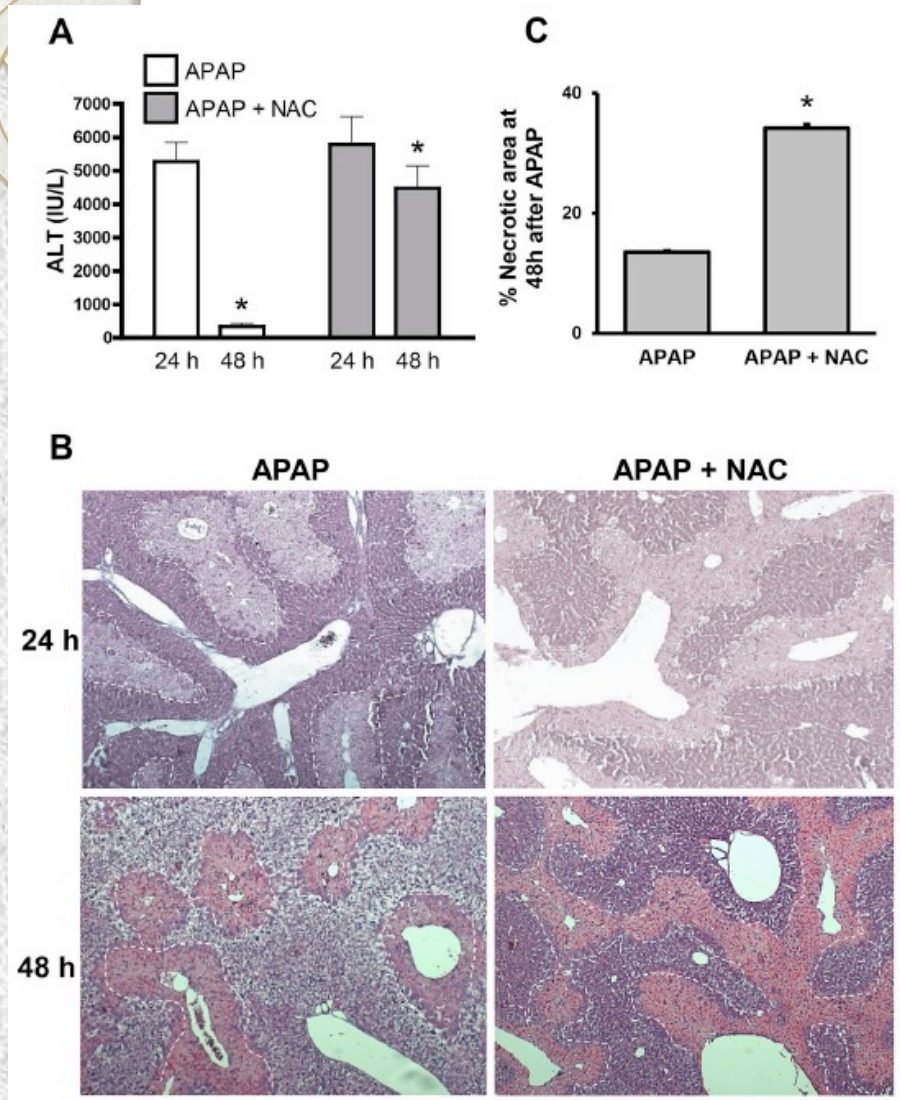
Antidotes to treat acetaminophen poisoning

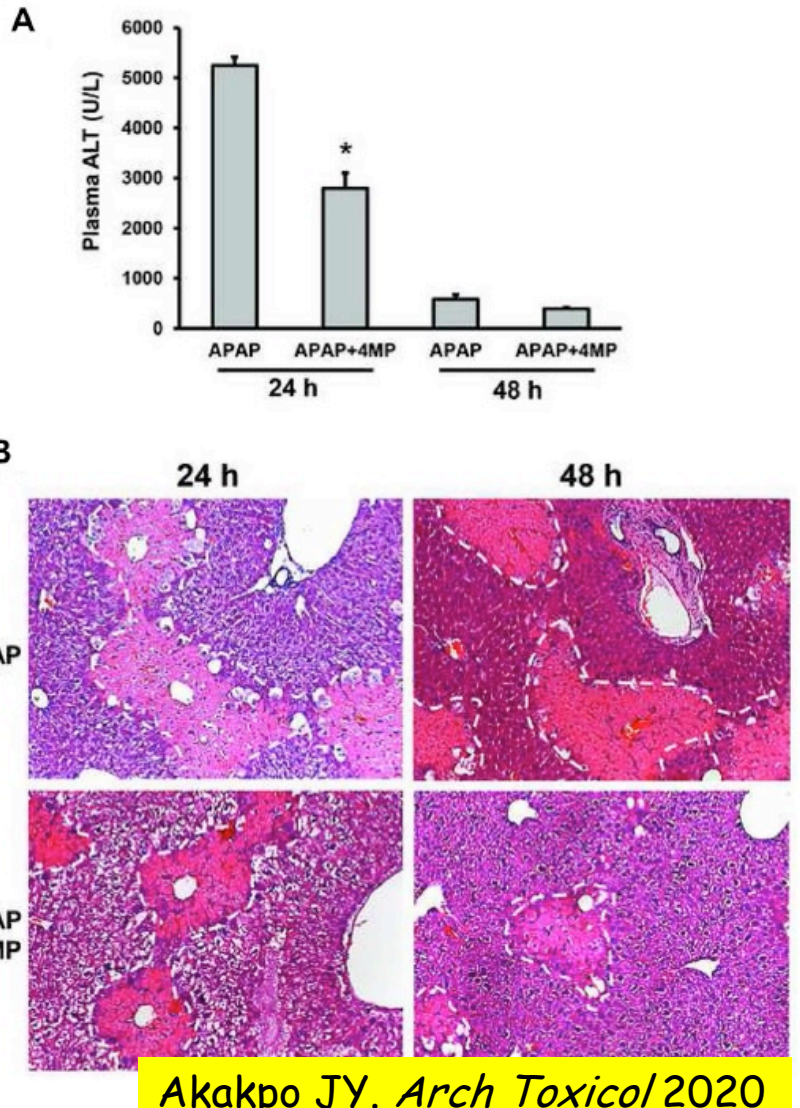
Novel therapeutic approaches against acetaminophen-induced liver Injury and acute liver failure



Jaeschke H. *Tox Sci* 2020

Delayed administration of NAC blunts recovery after an acetaminophen overdose unlike 4-methylpyrazole





Akakpo JY. *Arch Toxicol* 2020

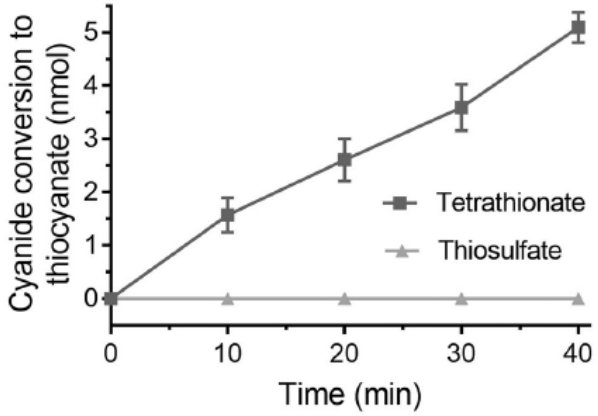
Antidotes to treat Cyanide poisoning

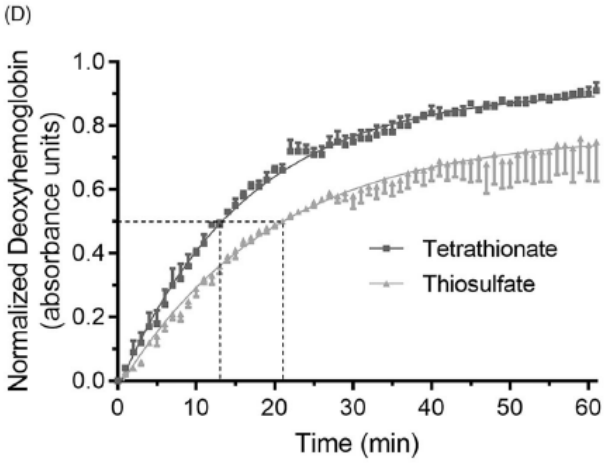
Sodium tetrathionate as CN antidote

$$Na_2S_4O_6 + CN^- \rightarrow SCN^- + SO_4^{-2} + Na_2S_2O_3$$

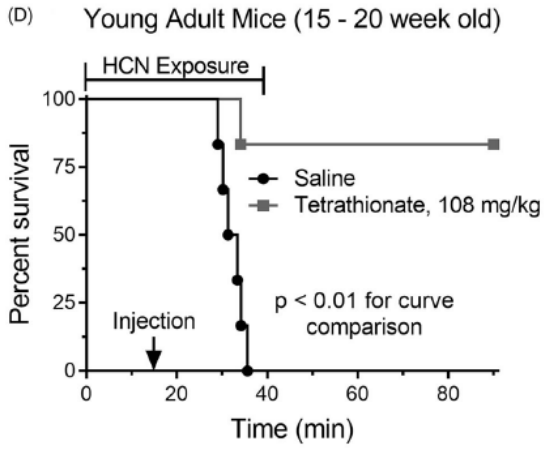
$$Na_2S_2O_3 + CN^- \xrightarrow{\text{Rhodanese}} SCN^- + SO_3^{-2}$$

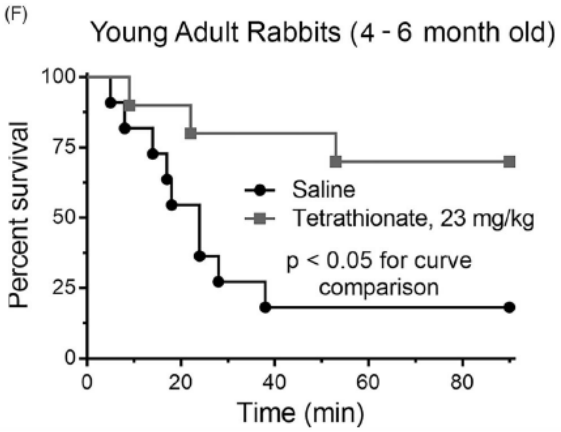
In vitro studies





In vivo studies

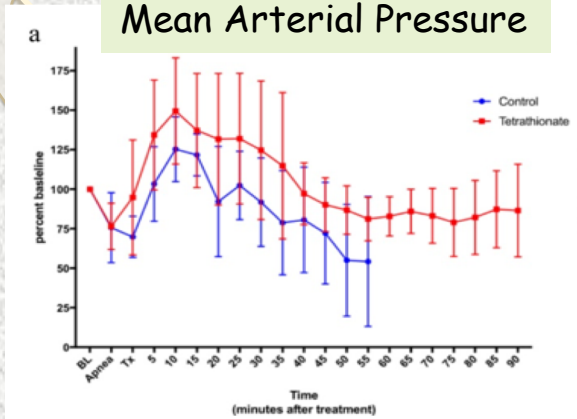




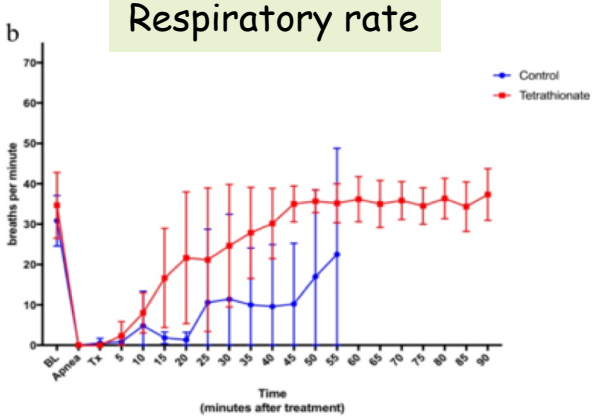
Caitlin T. *Clin Tox* 2021

Intramuscular sodium tetrathionate as antidote in a swine model of acute CN toxicity

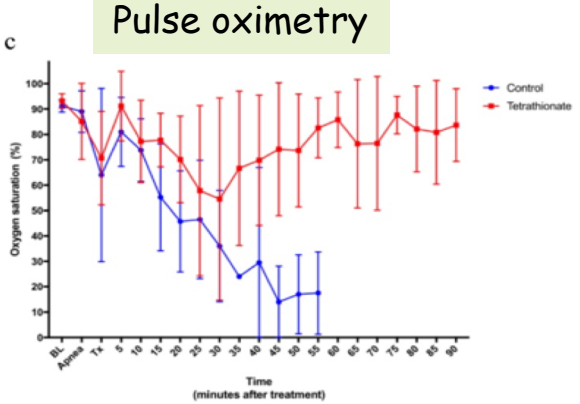
Mean Arterial Pressure



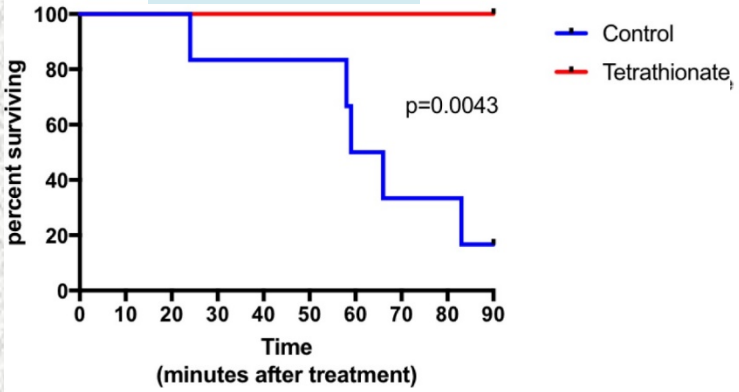
Respiratory rate



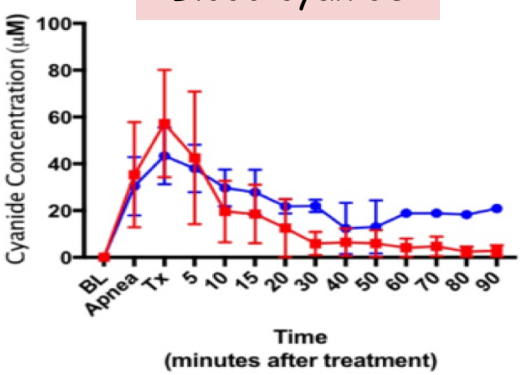
Pulse oximetry



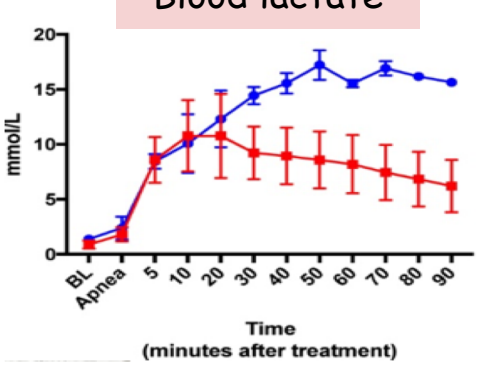
Survival rate

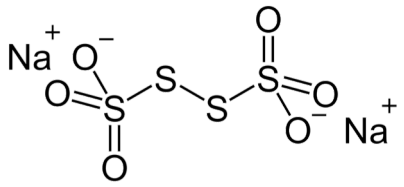


Blood cyanide



Blood lactate

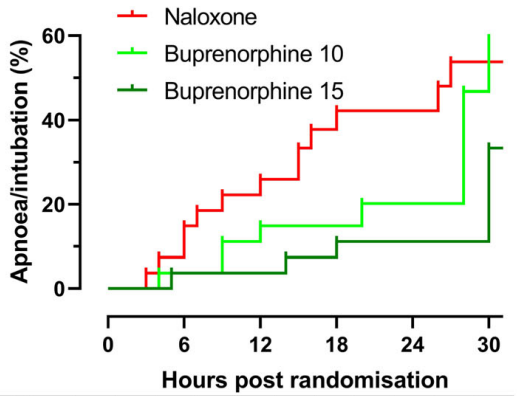




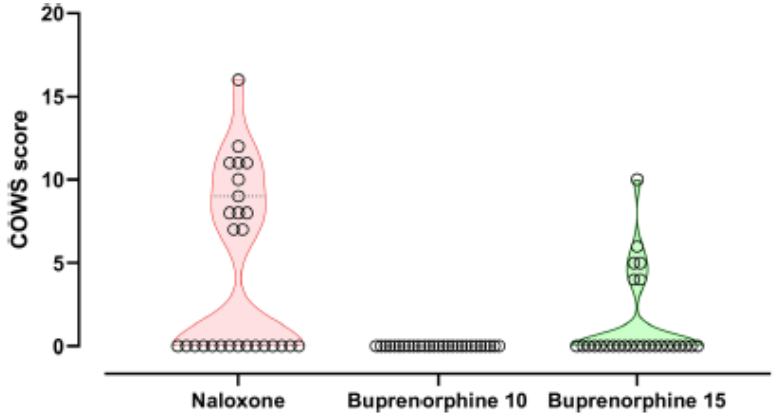
Hendry-Hofer TB. *Clin Tox* 2020

Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial

Outcome	Naloxone ($n = 27$)	Buprenorphine ($n = 54$)	P value
Response to bolus antidote doses	Complete 13 (48%) Partial 13 (48%) No response 1(4%)	Complete 50 (93%) Partial 3 (5%) No response 1 (2%)	< 0.0001
Opioid withdrawal	15 (56%)	6 (11%)	< 0.0001
Further apnea	6 (22%)	7 (13%)	0.34
Aspiration	1 (4%)	6 (11%)	0.41
Intubation	8 (30%)	5 (9%)	0.026
Continuing Sedation	9 (33%)	3 (6%)	0.002
ARDS	4 (15%)	0	0.01
Discharged alive with no sequelae (%)	23 (85%)	54 (100%)	0.01

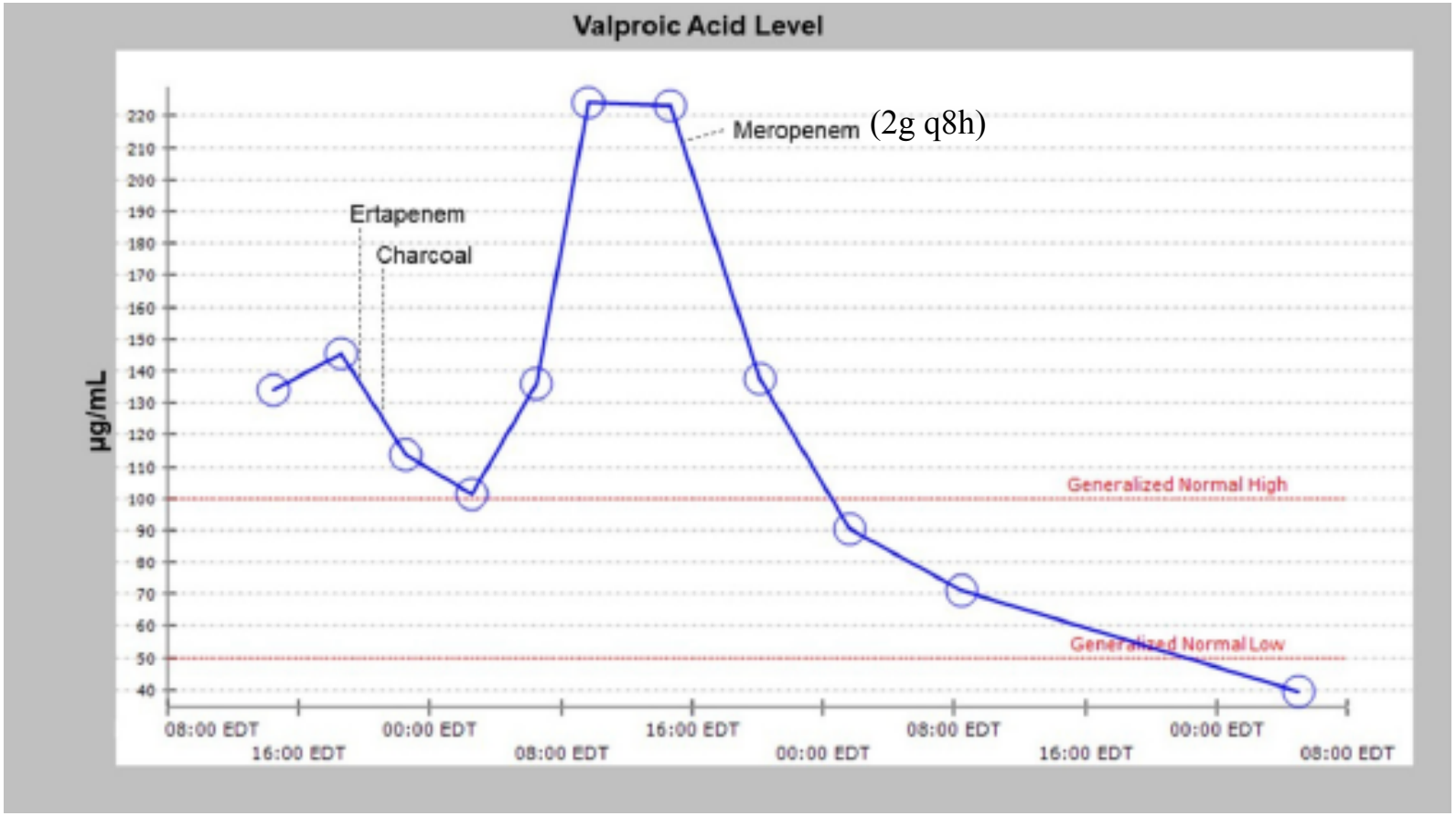


Number at risk											
Naloxone	27	27	25	22	23	21	20	14	11	9	9
Buprenorphine 10	27	27	27	26	25	24	22	19	15	9	2
Buprenorphine 15	27	27	27	27	27	27	26	25	21	9	4



Zamani N. *Crit Care* 2020

Meropenem as antidote for valproic acid overdose



Caitlin T. *Am J Emerg Med* 2019

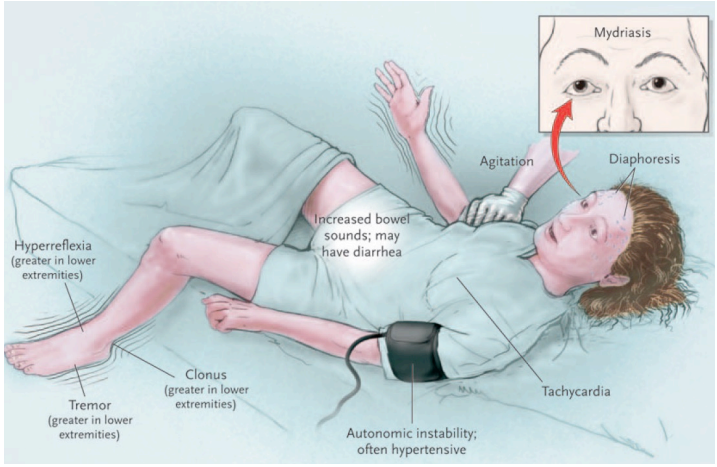
A case report

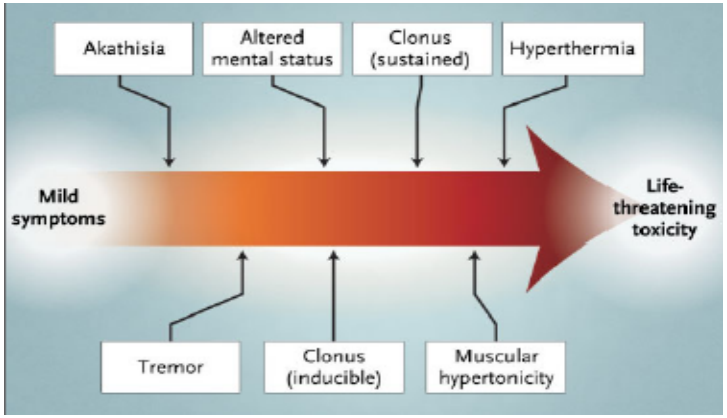
Marked and prolonged serotonin toxicity in a tramadol-poisoned patient with a pharmacokinetic study

A 21-year-old male self-ingested 750mg-tramadol, 200mg-sotalol, 400mg-propranolol and 6mg-lorazepam.

He was a kidney transplant patient treated with mycophenolate, tacrolimus, prednisone and paroxetine.

He developed prolonged serotonin toxicity requiring sedation, muscle paralysis and cyproheptadine, with favorable outcome





Bianconi G. *Clin Tox* 2021

Marked and prolonged serotonin toxicity in a tramadol-poisoned patient with a pharmacokinetic study

$T_{1/2}$

Tramadol (6.1h) and M1 (7.1h): N

M2 (26.5h) and M5 (16.7h): prolonged

Metabolic ratios

M1 x2-fold reduced

M2 x1,000-fold increased

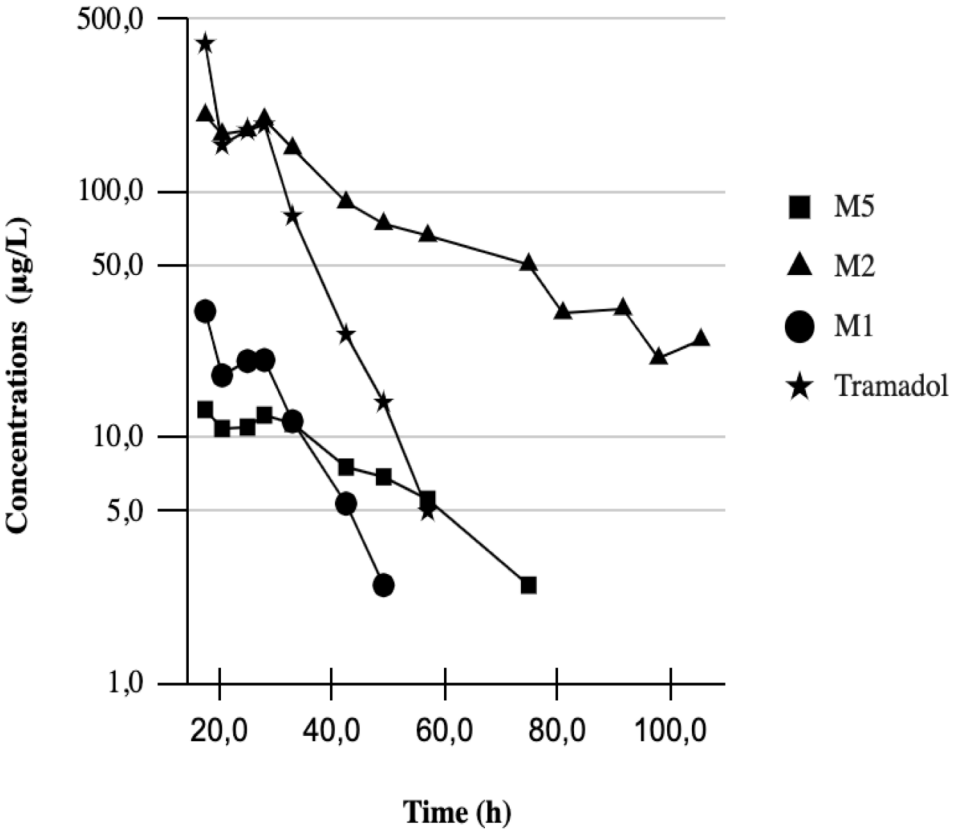
M5 normal

Genotyping

CYP2D6, 3A4, 2B6 metabolizer: N

➔ CYP2D6 inhibition by paroxetine and propranolol, two strong mechanism-based inhibitors.

➔ Only M2 present in sufficient concentrations up to 48h could explain the prolonged serotonin toxicity.



Bianconi G. *Clin Tox* 2021

How to investigate the case?

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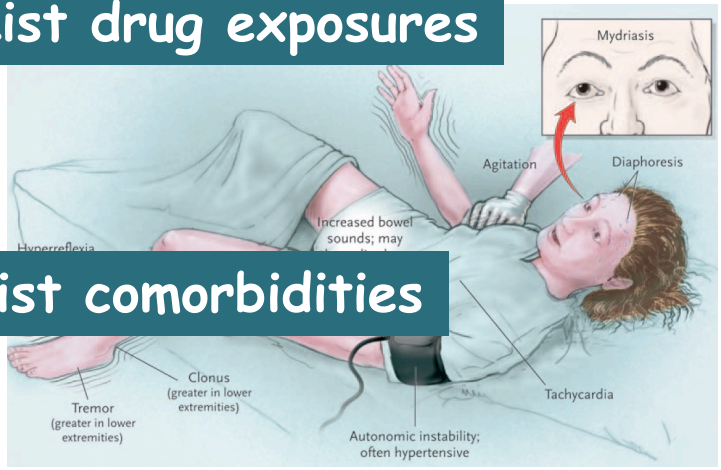
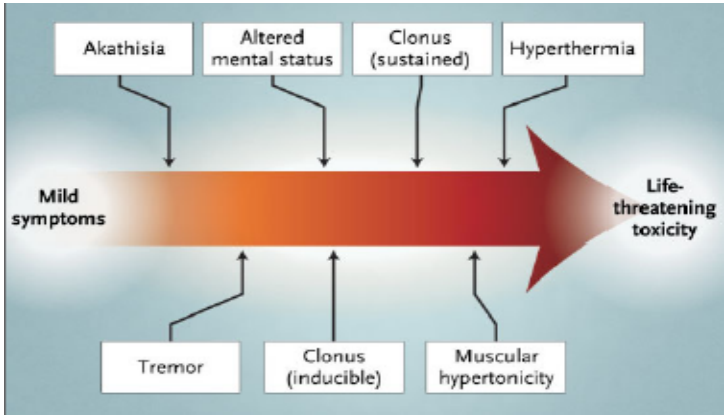
1- List drug exposures

2- List comorbidities

3- Identify the specificities of the clinical presentation





Bianconi G. *Clin Tox* 2021

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➔ CYP2D6 inhibition by paroxetine and propranolol, two strong mechanism-based inhibitors.
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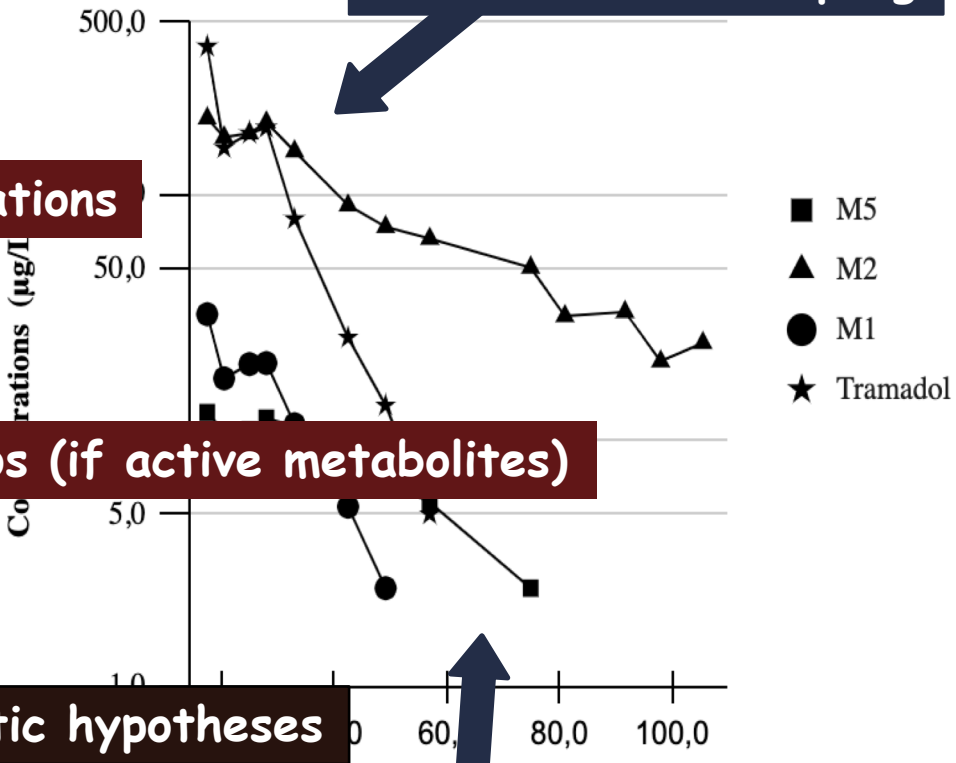
4- Blood/urine sampling



6- PK calculations

7- Metabolic ratios (if active metabolites)

8- Mechanistic hypotheses

5- Quantitative measurements

9- PK/PD correlations

Clin Tox 2021

Take home messages

- ✓ Even in emergency situation scientific strictness must be preserved
- ✓ **In medical toxicology**
  - ✓ Due to the rarity of some poisonings, case report are important and journals should continue to consider their publication.
  - ✓ Expert consensus are important but should take into account different local facilities
  - ✓ It is important to promote international multicenter prospective studies to have uniform data

How to be always updated on the toxicological literature?

- ✓ Subscribe the email alerts from toxicology/EM/IC journals
- ✓ follow the Twitter account of @EAPCCT
- ✓ #ToxReadingCorner with a new toxicological paper highlighted every two weeks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