Trends in Toxicology

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School of Medicine

Disclosure

- I have no direct or indirect financial interest in any company manufacturing or distributing any of the products discussed.

Which antidiabetic medication m cause or promote DKA in therapeuti use?

Liraglutide	A
Canagliflozin	B
Sitagliptin	C
ateglinide	D

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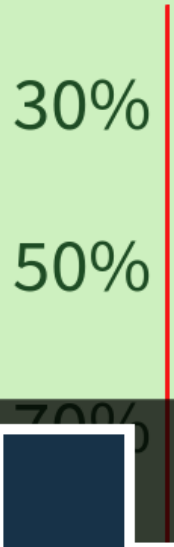
When following the package ins instruction for preparing IV N-acetylcysteine (Acetadote ®), how often will the resulting solution have the intended dose (with 10%).



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A 25 y/o man presents with nausea, vomiti
abdominal pain. He has history of cyclic vo
His social history includes occasional alcohol us
and daily marijuana but no other iliicit drugs. His labs show elevated BUN/Cr ratio and elevated urine Spec Grav, but otherwise normal CMP. The treatment least likely to relieve symptoms is:

Prochlorperazine

Ondansetron

Capsaicin

shower

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For a 65 y/o woman weighing 100 kg ha stable on Digoxin for several years. She presents feeling unwell and has sinus bradycardia at 52, [K+] of 5.4 mmol/L, [creatinine] of 1.6 mg/dL (140 umol/L) and serum [digoxin] of 4 ng/mL. The dose of Digoxin Fab fragments should be:

1 vial (40 mg)

2 vials (80 mg)

ls (160 mg)

20 mg)

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A patient chronically taking lithi carbonate for bipolar disorder takes deliberate overdose of his own medication. His BMP shows no indication of AKI. What laboratory result should motivate hemodialysis?

[Li+] > 2.5 mmol/L

[Li+] > 3.6 mmol/L

[Li+] > 4.0 mmol/L

1 mmol/L

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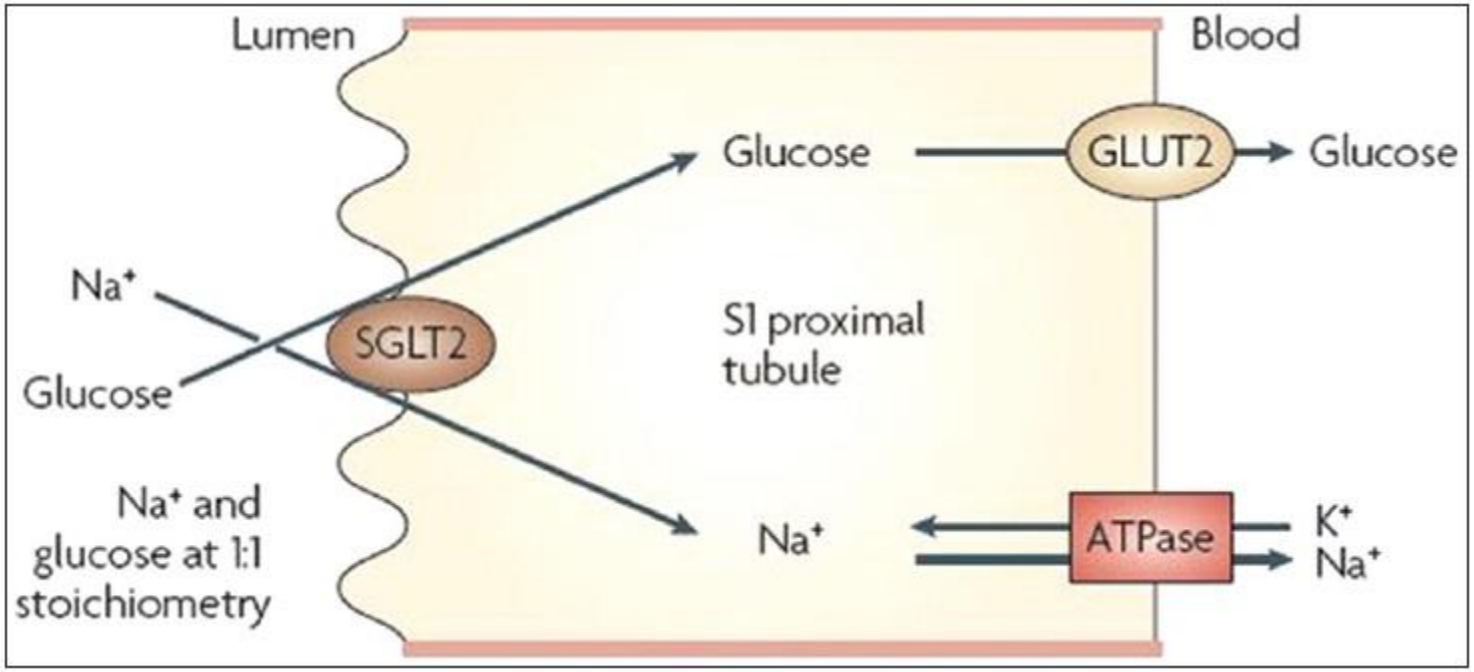
Objectives

- Describe two potential adverse drug reactions associated with newer antidiabetic medications.
- Describe the key features and potential treatments for cannabinoid hyperemesis syndrome (CHS)
- Propose a safer and more consistent method of antidotal treatment for acetaminophen toxicity.
- Discuss recent literature regarding antidotal treatment of digoxin toxicity
- Discuss recent literature on thresholds for dialysis for treatment of lithium toxicity.

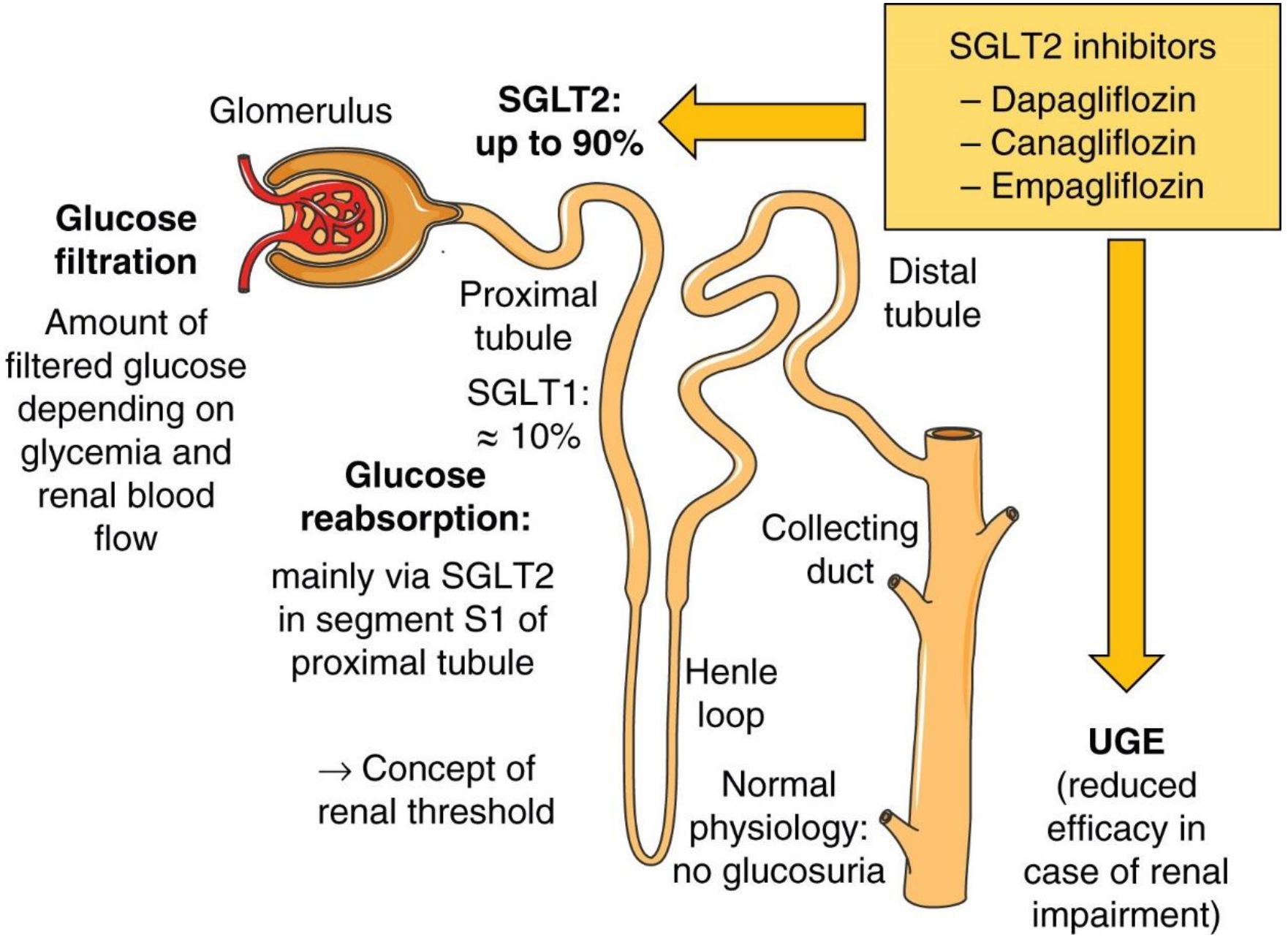
Antidiabetic drugs: new drugs, new problems

- Canagliflozin
- Empagliflozin
- Dapagliflozin
- Remogliflozin
- Sotagliflozin
- Sitagliptin
- Saxagliptin
- Linagliptin
- Vildagliptin

Sodium Glucose Transporter-2 Inhibitors



- Canagliflozin (Invokana®)
- Dapagliflozin (Farxiga®)
- Empagliflozin (Jardiance®)
- Plus several more “-agliflozins” in development

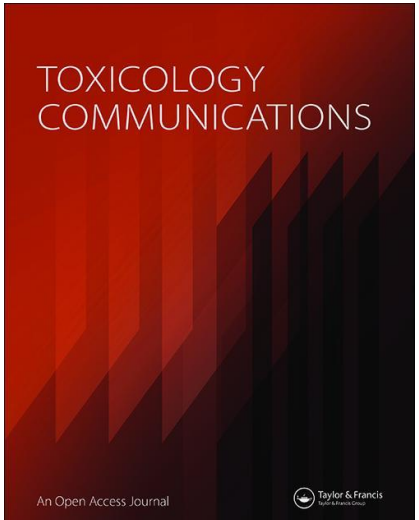


Scheen AJ. Evaluating SGLT2 inhibitors for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert Opin Drug Metab Toxicol*. (2014;10(5):647-663

55 y/o F with T2DM on canagliflozin 300 mg daily.

Nausea, vomiting, polyuria over 24 h, tachycardia, hypotension, dry mucosa & epigastric abdominal pain.

	Time after presentation (hours)				
Patient 1	**0**	**3**	**6.5**	**10**	**12**
Na+ (mmol/L)	142	146	148	144	142
K+ (mmol/L)	4.3	4.2	4.5	4	4.6
Cl- (mmol/L)	102	115	119	117	117
HCO3- (mmol/L)	**8***	**10***	**12***	17	17
Anion gap	**32***	**21***	**17***	10	8
BUN (mg/dL)	43	39	34	31	27
Creatinine (mg/dL)	1.92*	1.31*	1.16*	0.98	0.88
Glucose (mg/dL)	**366***	**287***	–	–	–
B-OHB (mmol/L)	**12.43***		–	–	–
AST (IU/L)	18	12	–	–	–
ALT (IU/L)	27	18	–	–	–
Lipase (U/L)	164*	–	–		
VBG pH	**7.09***	–	–		
VBG pCO_2 (mmHg)	**29***	–	–		
VBG pO_2 (mmHg)	44	–	–		
VBG HCO_3 (mmol/L)	**8.8***	–	–		



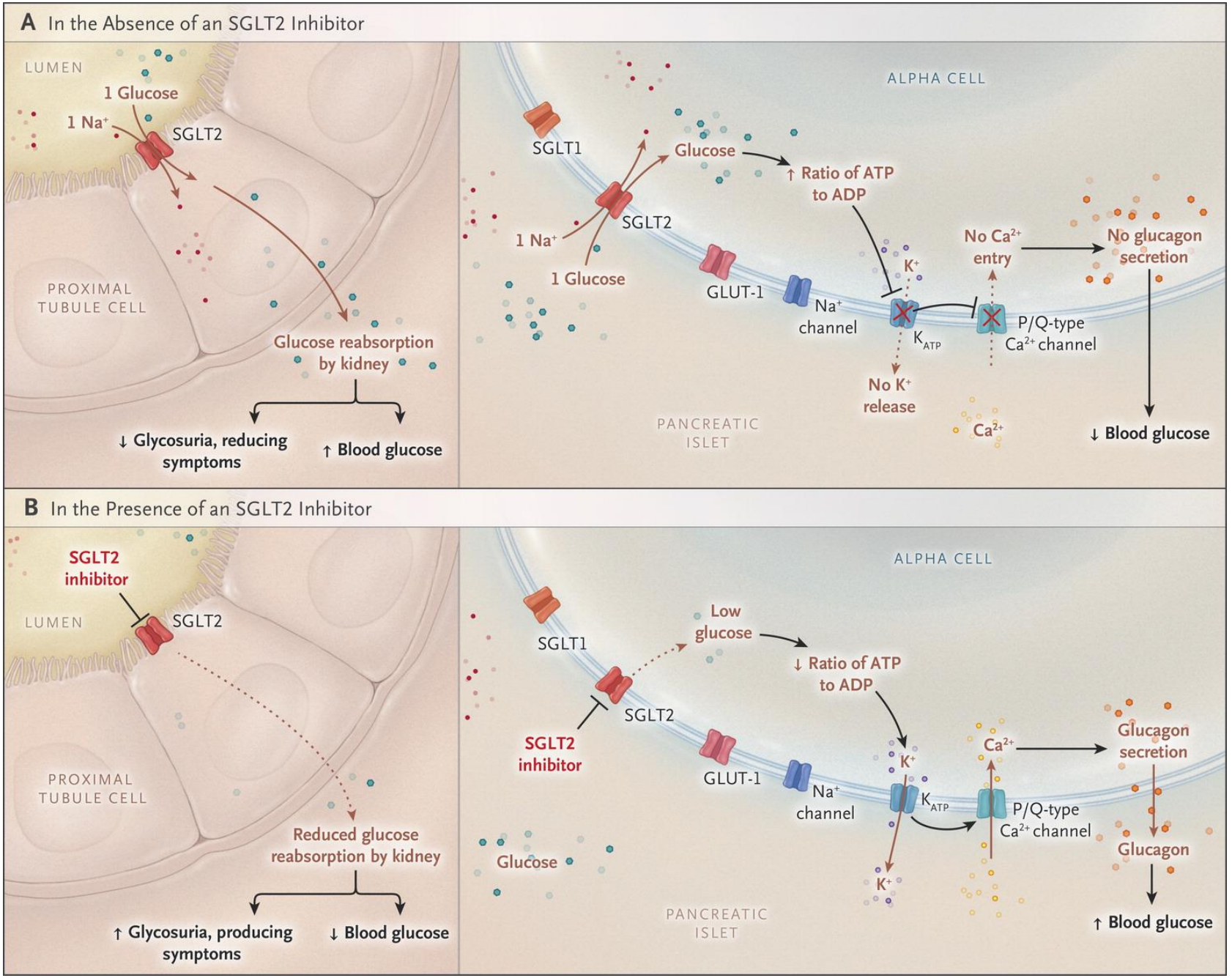
Chai PR, Bonney C, Blohm E, Boyer EW, Babu KM. Canagliflozin-associated diabetic ketoacidosis: a case report. *Toxicol Commun* 2017; 1(1):2-5.

54 y/o M T1DM on Humalog 25/35 units SQ BID, Albiglutide 50 mg daily, & Canagliflozin 300 mg daily.

Abdominal pain, nausea, vomiting, tachycardia, tachypnea. His dry mucosa & epigastric tenderness.

	Time after presentation (hours)				
Patient 2	**0**	**2.5**	**5**	**8**	**14**
Na+ (mmol/L)	137	138	134	134	132
K+ (mmol/L)	4.7	4.5	4.1	3.9	4.2
Cl- (mmol/L)	102	112	–	111	110
HCO3- (mmol/L)	**8***	**11***	**9***	16	20
Anion gap	**27***	**15***	–	7	2
BUN (mg/dL)	19	15	12	9	6
Creatinine (mg/dL)	0.76	0.65	0.71	0.62	0.48
Glucose (mg/dL)	**327***	**249***	**334***	**235***	103
B-OHB (mmol/L)	**15.35***	–	–	–	–
AST (IU/L)		–	8	–	–
ALT (IU/L)	–	–	8	–	–
Lipase (U/L)	–	–	14	–	–
VBG pH	**7.15***	–	**7.15***	–	–
VBG pCO_2 (mmHg)	**29***	–	**30***	–	–
VBG pO_2 (mmHg)	81	–	65	–	–
VBG HCO_3 (mmol/L)	**10***	–	**10.2***	–	–

Chai PR, Bonney C, Blohm E, Boyer EW, Babu KM. Canagliflozin-associated diabetic ketoacidosis: a case report. *Toxicol Commun* 2017; 1(1):2-5.



Hattersley AT, Thorens B. Type 2 Diabetes, SGLT2 inhibitors, and glucose secretion. *N Engl J Med* 2015;373:974-976.

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Cascade of clinical events and metabolic changes leading to euDKA.

Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 Inhibitors. *Diabetes Care* 2015;38:1638-1642

- DKA and related events (ketoacidosis, metabolic acidosis, and acidosis) from 17,596 patients from randomized studies of canagliflozin through 11 May 2015.

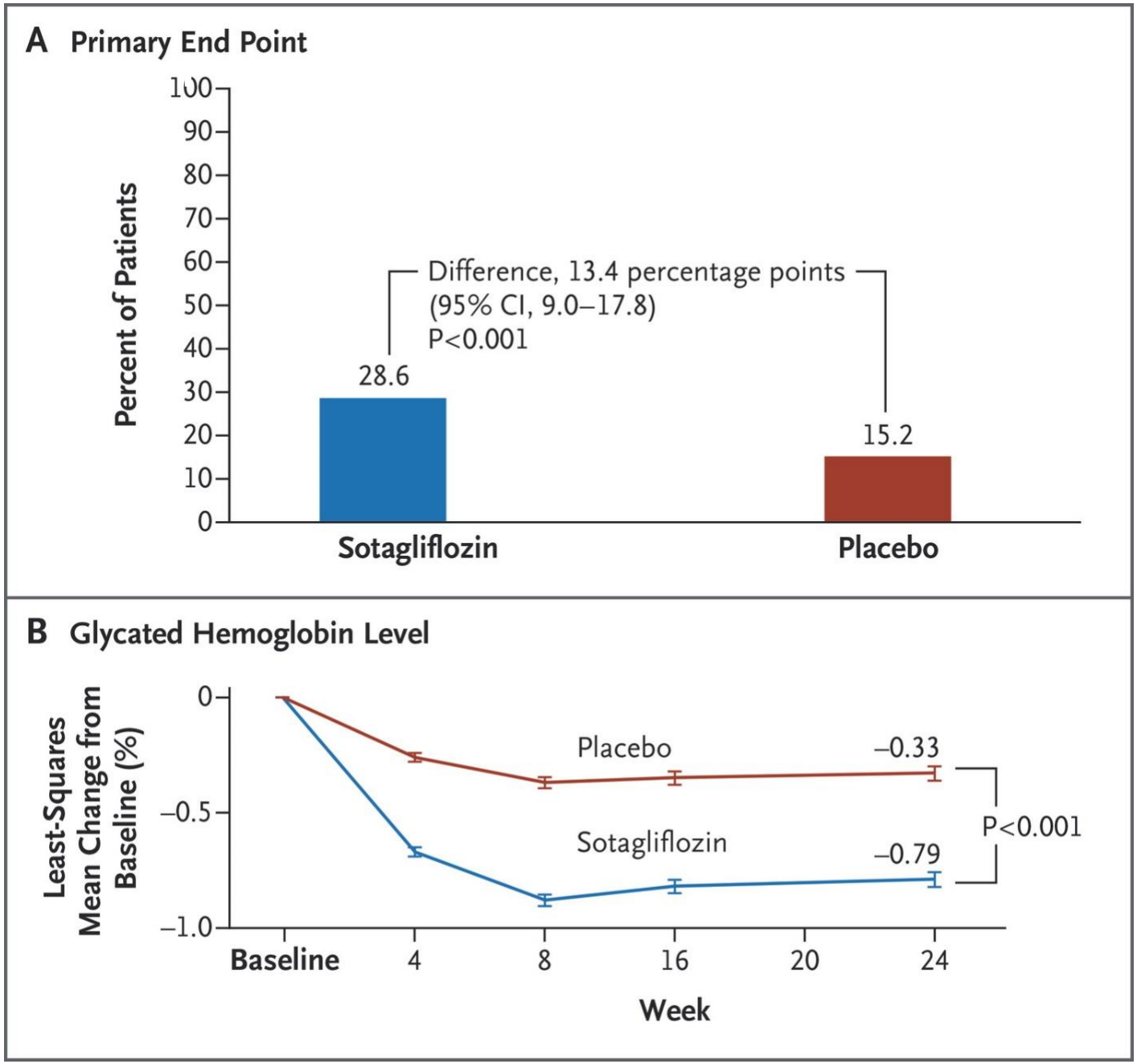
	Canagliflozin 100 qD	Canagliflozin 300 qD	Comparator*
Incidence (%)	0.07	0.11	0.03
Events/10^3 Pt-yr	0.522	0.763	0.238

**Placebo, Sitagliptin, Metformin, Glimepiride*

~ 1 / 1000

- Most patients with DKA had a blood glucose >300 mg/dL.

Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the Canagliflozin Type 2 Diabetes Clinical Program. *Diabetes Care* 2015;38(9):1680-1686.



Garg SK et al. Effects of sotagliflozin added to insulin in patients with Type 1 diabetes. N Engl J Med 2017. DOI: 10.1056/NEJMoa1708337

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Table 3. Summary of Adverse Events.*

Event	Sotagliflozin (N=699)	Placebo (N=703)
	no. of patients (%)	
Adverse events		
Any adverse event	385 (55.1)	369 (52.5)
Serious adverse event	48 (6.9)	23 (3.3)
Severe adverse event	16 (2.3)	9 (1.3)
Death	1 (0.1)†	0
Positively adjudicated adverse events		
Severe hypoglycemia, ≥1 episode‡	21 (3.0)	17 (2.4)
Severe nocturnal hypoglycemia, ≥1 episode‡	2 (0.3)	5 (0.7)
Severe hypoglycemia in a patient who used insulin pump, ≥1 episode§	10 (3.6)	5 (1.8)
Severe hypoglycemia in a patient who did not use insulin pump, ≥1 episode§	11 (2.6)	12 (2.8)
Diabetic ketoacidosis, ≥1 episode	21 (3.0)	4 (0.6)
Diabetic ketoacidosis in a patient who used insulin pump, ≥1 episode§	12 (4.4)	2 (0.7)
Diabetic ketoacidosis in a patient who did not use insulin pump, ≥1 episode§	9 (2.1)	2 (0.5)
Major adverse cardiovascular events	2 (0.3)	0
Myocardial infarction	1 (0.1)	0
Stroke	0	0
Hospitalization due to heart failure	0	0
Coronary revascularization	1 (0.1)	0
Liver injury	0	0
Investigator-reported events of special interest		
Volume depletion	13 (1.9)	2 (0.3)
Genital mycotic infection	45 (6.4)	15 (2.1)
Urinary tract infection	25 (3.6)	27 (3.8)
Diarrhea¶	29 (4.1)	16 (2.3)
Pancreatitis	0	0
Bone fracture	4 (0.6)	5 (0.7)
Potential drug-induced liver injury	2 (0.3)	0
Renal event	5 (0.7)	3 (0.4)
Cancer	1 (0.1)	2 (0.3)
Documented hypoglycemia‡	673 (96.3)	670 (95.3)
Documented nocturnal hypoglycemia‡	521 (74.5)	553 (78.7)
Blood glucose ≤55 mg/dl during self-monitoring	528 (75.5)	559 (79.5)
Hypoglycemic events‖		
Blood glucose ≤70 mg/dl during self-monitoring	69.8	77.9
Blood glucose ≤55 mg/dl during self-monitoring	11.8	15.4
Serious and nonserious acidosis-related adverse events	60 (8.6)	17 (2.4)
Serious acidosis-related adverse events	24 (3.4)	5 (0.7)
Nonserious acidosis-related adverse events	39 (5.6)	12 (1.7)
Positively adjudicated serious and nonserious acidosis-related adverse events	23 (3.3)	4 (0.6)
Positively adjudicated acidosis-related events that were also classified as diabetic ketoacidosis	21 (3.0)	4 (0.6)
Events that led to discontinuation		
Any adverse event that led to discontinuation	44 (6.3)	16 (2.3)
Any event of special interest that led to discontinuation**	21 (3.0)	5 (0.7)
Diarrhea	3 (0.4)	0
Genital mycotic infection	2 (0.3)	0
Urinary tract infection	0	2 (0.3)
Penile infection	1 (0.1)	0
Vulvovaginal candidiasis	1 (0.1)	0
Wrist fracture	1 (0.1)	0
Increase in hepatic enzyme	1 (0.1)	0
Severe hypoglycemia‡	2 (0.3)	1 (0.1)
Diabetic ketoacidosis	11 (1.6)	1 (0.1)
Acetonemia	1 (0.1)	0
Neoplasm	0	1 (0.1)
Renal failure	0	1 (0.1)

Positively adjudicated adverse events		
Severe hypoglycemia, ≥1 episode‡	21 (3.0)	17 (2.4)
Severe nocturnal hypoglycemia, ≥1 episode‡	2 (0.3)	5 (0.7)
Severe hypoglycemia in a patient who used insulin pump, ≥1 episode§	10 (3.6)	5 (1.8)
Severe hypoglycemia in a patient who did not use insulin pump, ≥1 episode§	11 (2.6)	12 (2.8)
Diabetic ketoacidosis, ≥1 episode	21 (3.0)	4 (0.6)
Diabetic ketoacidosis in a patient who used insulin pump, ≥1 episode§	12 (4.4)	2 (0.7)
Diabetic ketoacidosis in a patient who did not use insulin pump, ≥1 episode§	9 (2.1)	2 (0.5)

$$OR = (A * D)/(B * C)$$

$$OR = (21 * 699)/ (4 * 678)$$

$$OR = 5.4 \text{ for DKA on sotagliflozin}$$

Garg SK et al. Effects of sotagliflozin added to insulin in patients with Type 1 diabetes. N Engl J Med 2017. DOI: 10.1056/NEJMoa1708337

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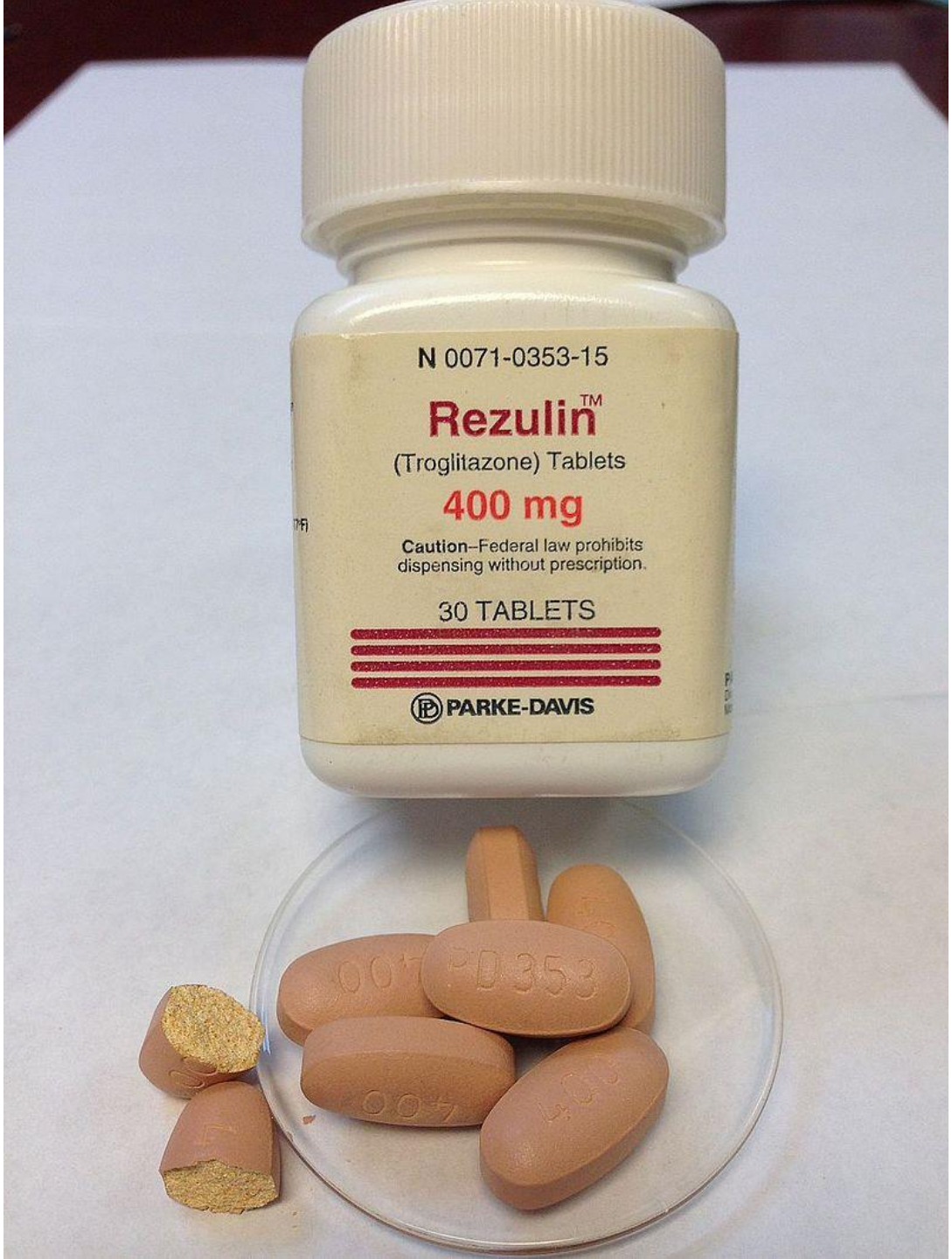
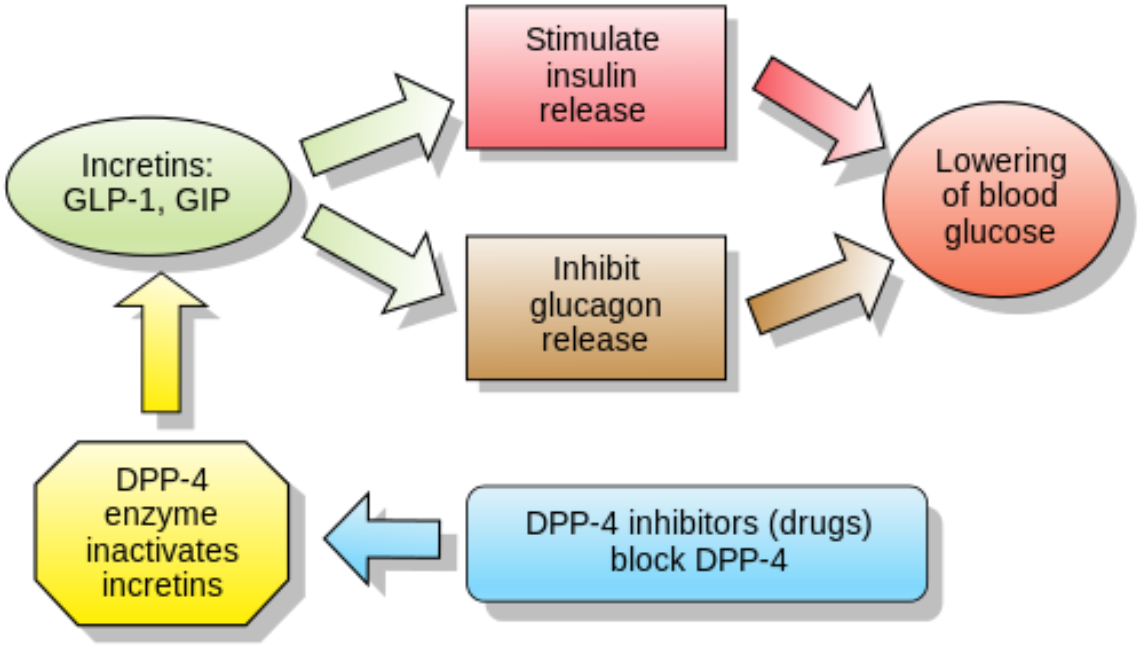
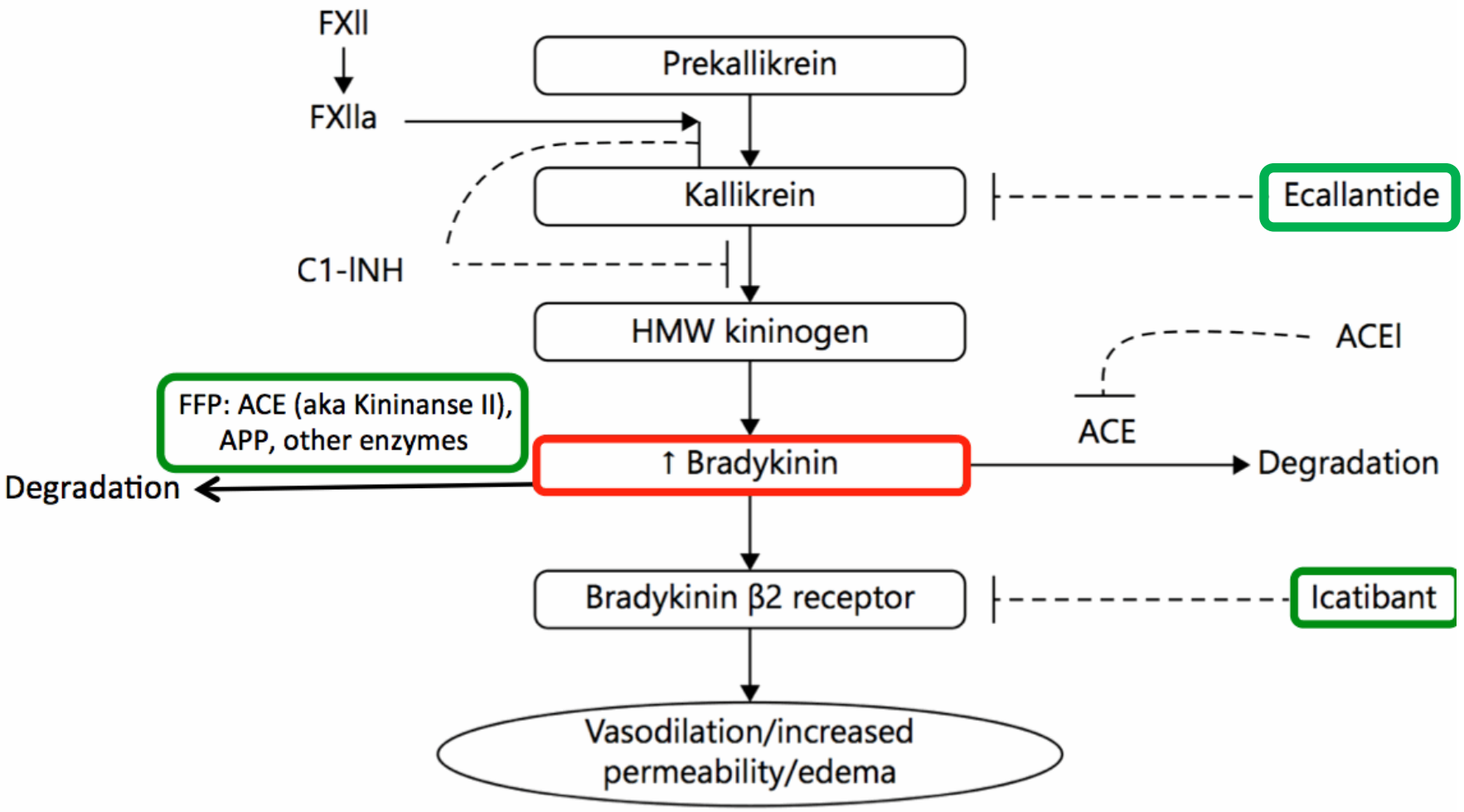

N 0071-0353-15
Rezulin™
(Troglitazone) Tablets
400 mg
Caution–Federal law prohibits dispensing without prescription.
30 TABLETS
PARKE-DAVIS
0071 PD 353

Dipeptidyl Peptidase-4 inhibitors

Sitagliptin (Januvia®)
Linagliptin (Trajenta®)
Saxagliptin (Onglyza®)
Vildagliptin (Galvus®)
Alogliptin (Nesina®)



DPP-4 catabolizes Bradykinin and Substance P.



Craig et al. Int Arch Allergy Immunol 2014;165:119-127

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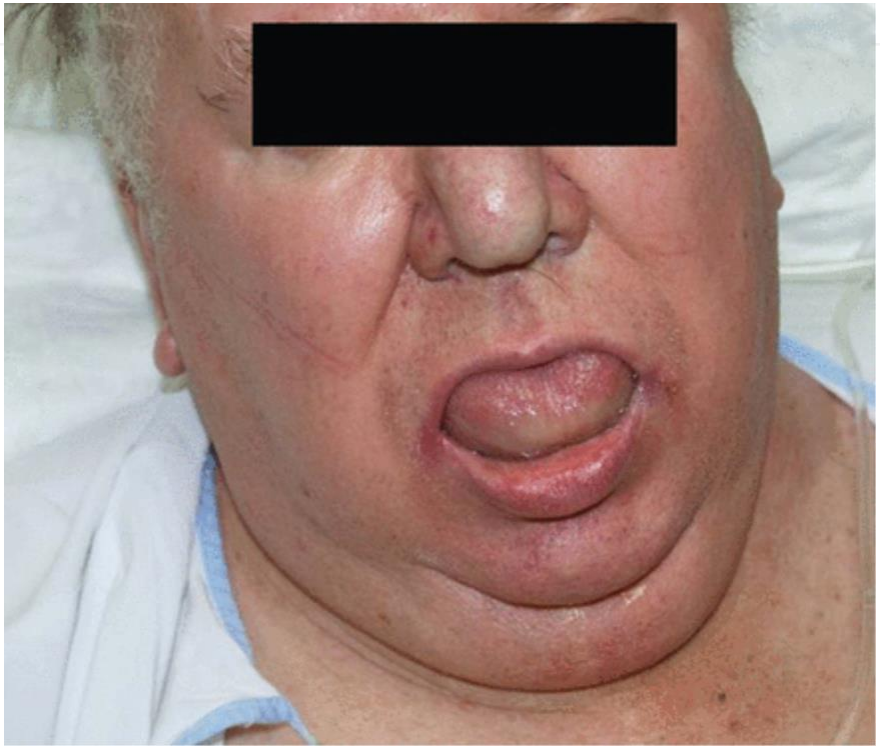
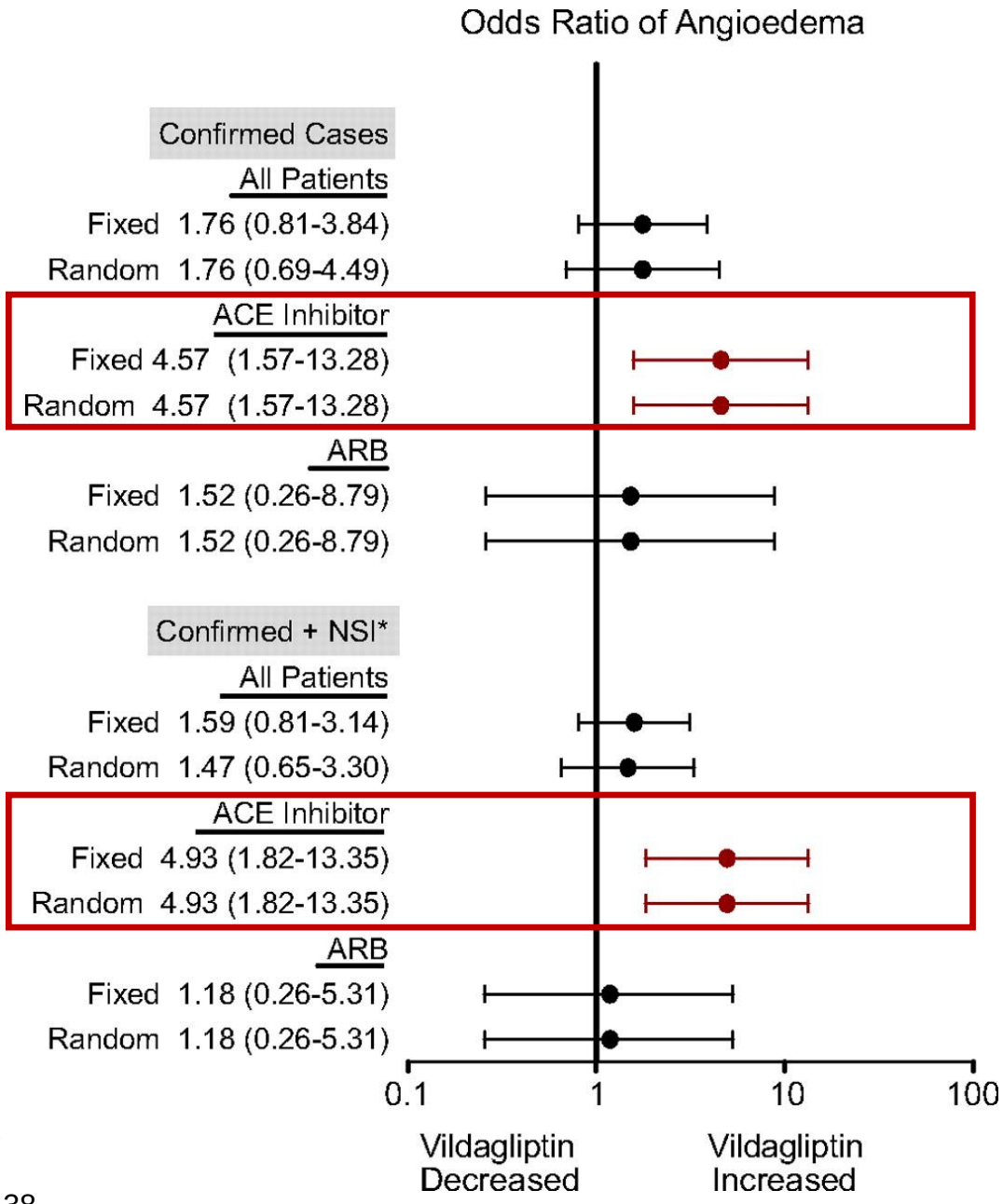


Treatment of a life-threatening laryngeal bradykinin angio-oedema precipitated by dipeptidylpeptidase-4 inhibitor and angiotensin-I converting enzyme inhibitor with prothrombin complex concentrates. *Br J Anaesth*. 2012;109(5):827-829. doi:10.1093/bja/aes371

- DPP-4 inhibitor may increase risk of ACEI-Angioedema
- 4½ to 5 fold increase in risk with Vildagliptin and ACE-I.
- Class effect?



Byrd JS et al *J Allergy Clin Immunol* 2007;120:403-408
Brown NJ et al Hypertension. 2009;54:516-523
Byrd JS et al, *Ann All Asthma Immunol* 2011;106:436-438

Joint Pains

Presentation

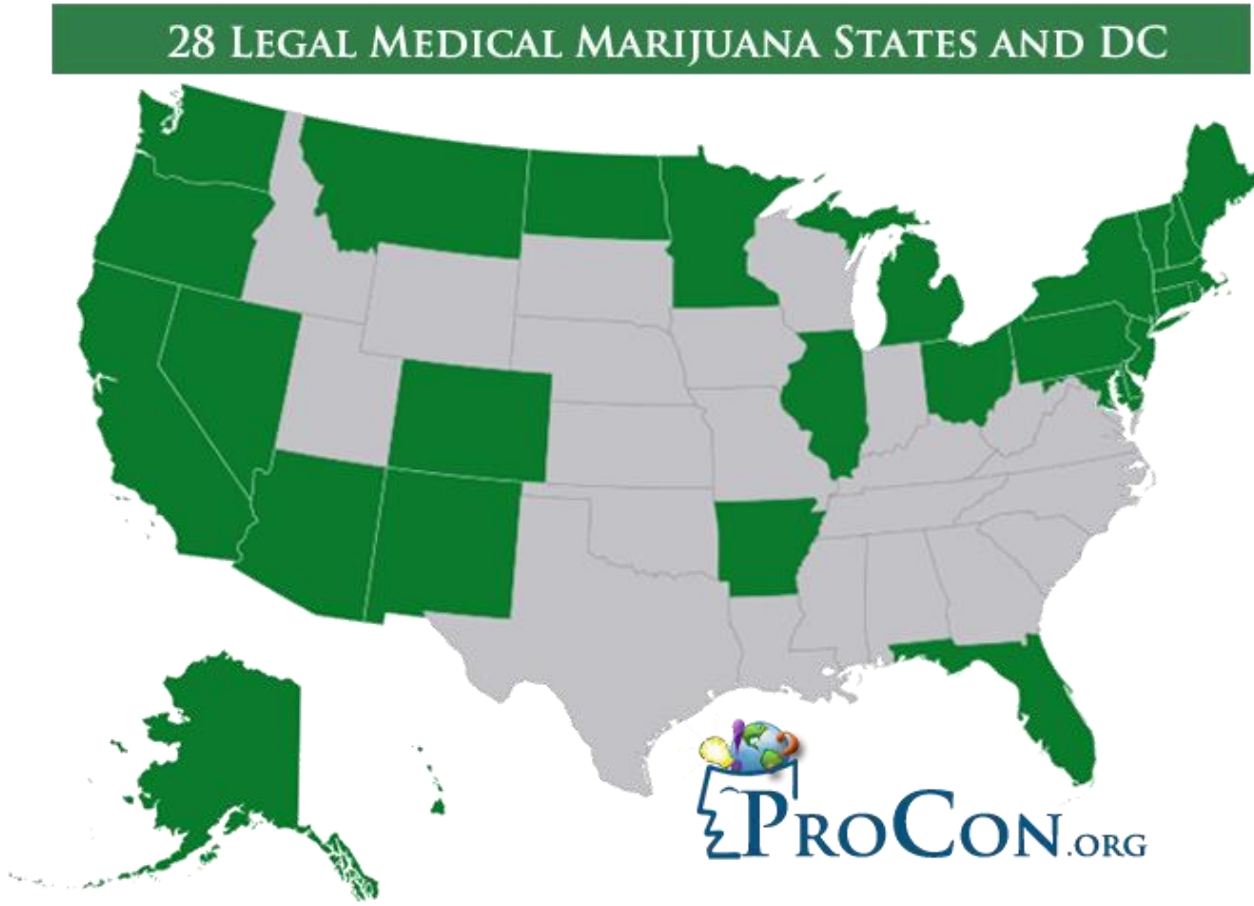
- 28 y/o M presents with abdominal pain, nausea, intermittent vomiting for 2 days.
- Had similar visit to another hospital twice in the past 2 months.
- “They couldn’t find out what’s wrong, so I came here. They gave something that started with ‘D’. It helped for a while.”

Initial work-up

- IV fluid bolus
- Ondansetron 4 mg IVP
- CBC, BMP, LFTs, Lipase, UA

- Heart rate slightly lower
- 2+ urine ketones
- Nausea not improved
- Still having “10/10” abdominal pain.
- Asks if he can have a shower.

- Prochlorperazine 10 mg IVP
  - reports slightly more relief.



- Increase in legal use of cannabis
- Increase in potency of available cannabis products
- Last decade of recognition of cyclic vomiting and abdominal pain in association with daily cannabis use

Cannabinoid Hyperemesis Syndrome

CHS

Cause:

Heavy, long-term use

CHS

Relieved by:

Hot showers, baths

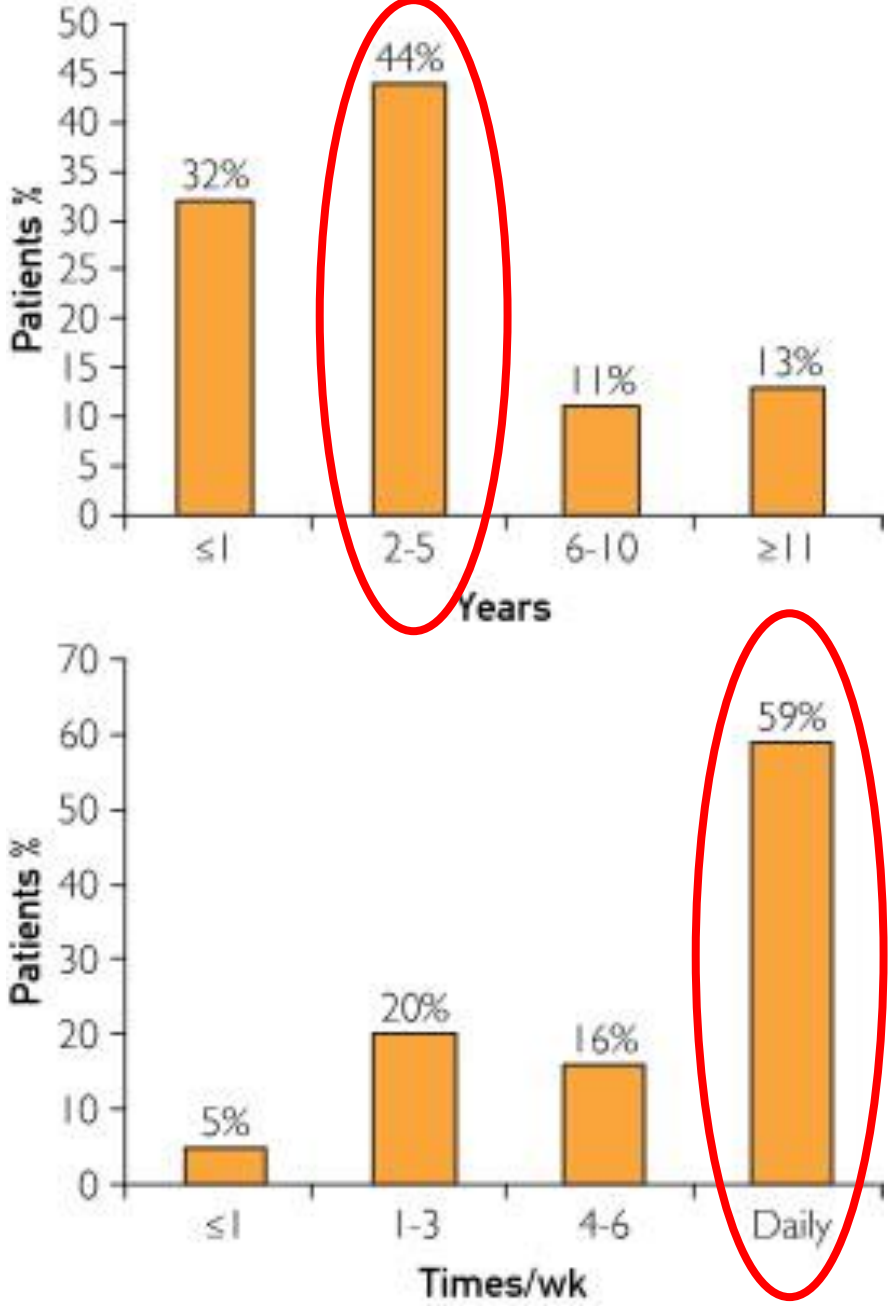
Proposed Clinical Criteria for Cannabinoid Hyperemesis

Essential for diagnosis	Long-term cannabis use
Major features	Severe cyclic nausea and vomiting Resolution with cannabis cessation Relief of symptoms with hot showers or baths Abdominal pain, epigastric or periumbilical Weekly use of marijuana
Supportive features	Age less than 50 y Weight loss of >5 kg Morning predominance of symptoms Normal bowel habits Negative laboratory, radiographic, endoscopic test results

Simonetto, DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clin Proc*. 2012; 87: 114–119.

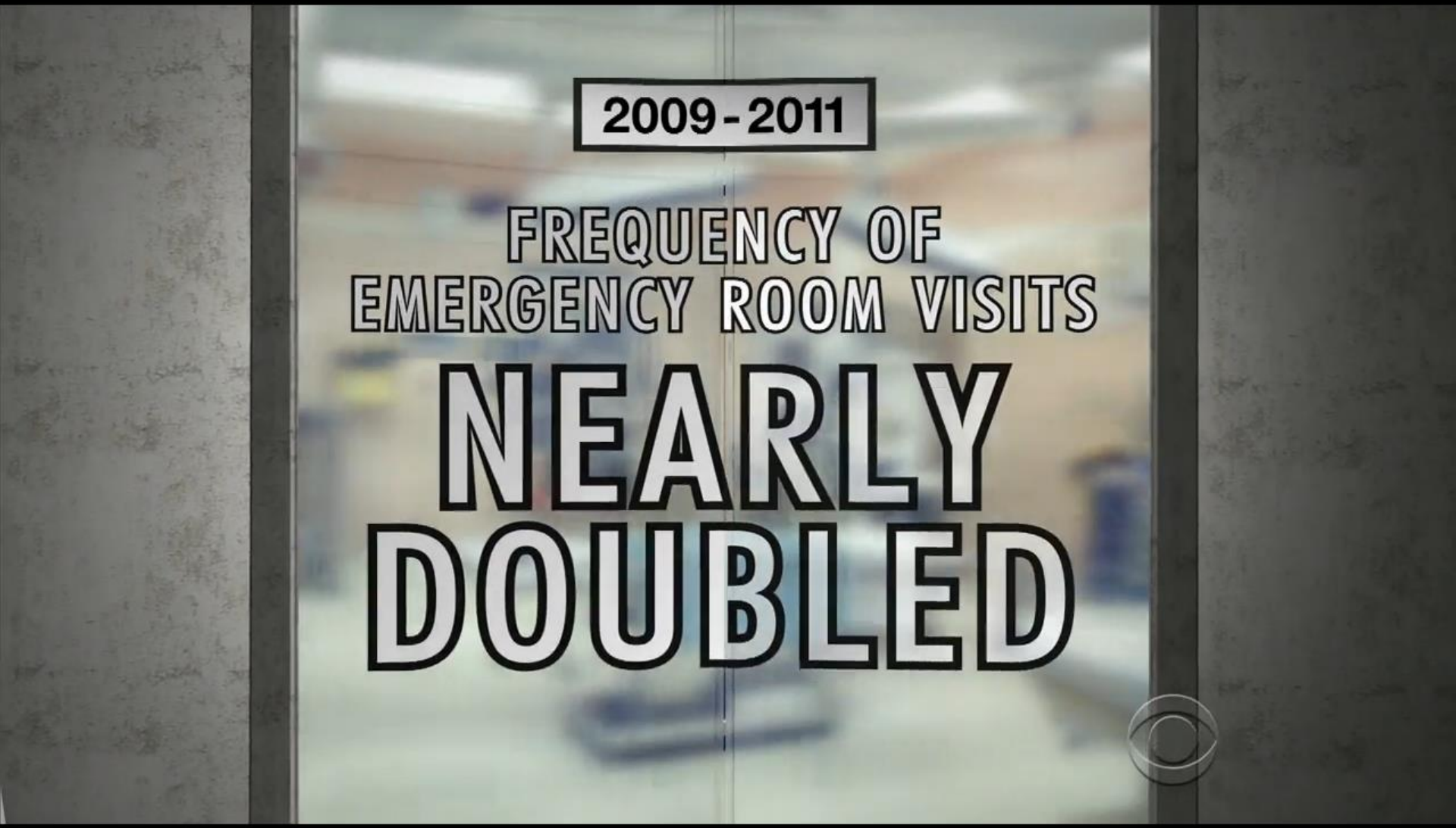
Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review. *J Med Toxicol* 2017;13(1):71–87

MAYO CLINIC



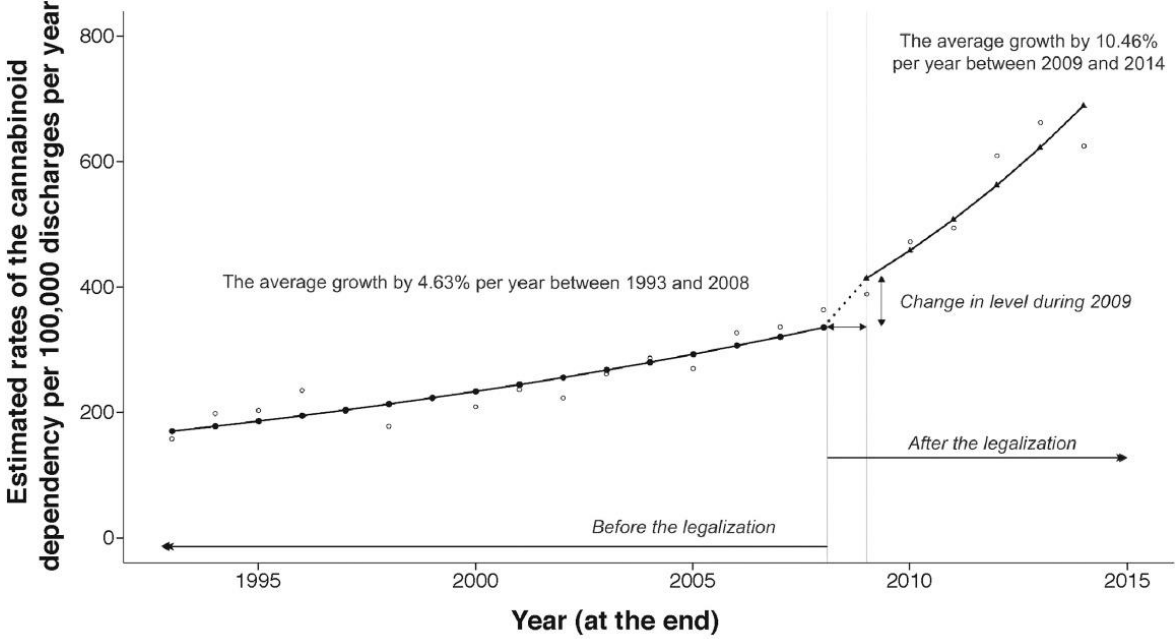
Simonetto, D.A., Oxentenko, A.S., Herman, M.L., and Szostek, J.H. Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clin Proc*. 2012; 87: 114–119

MAYO CLINIC

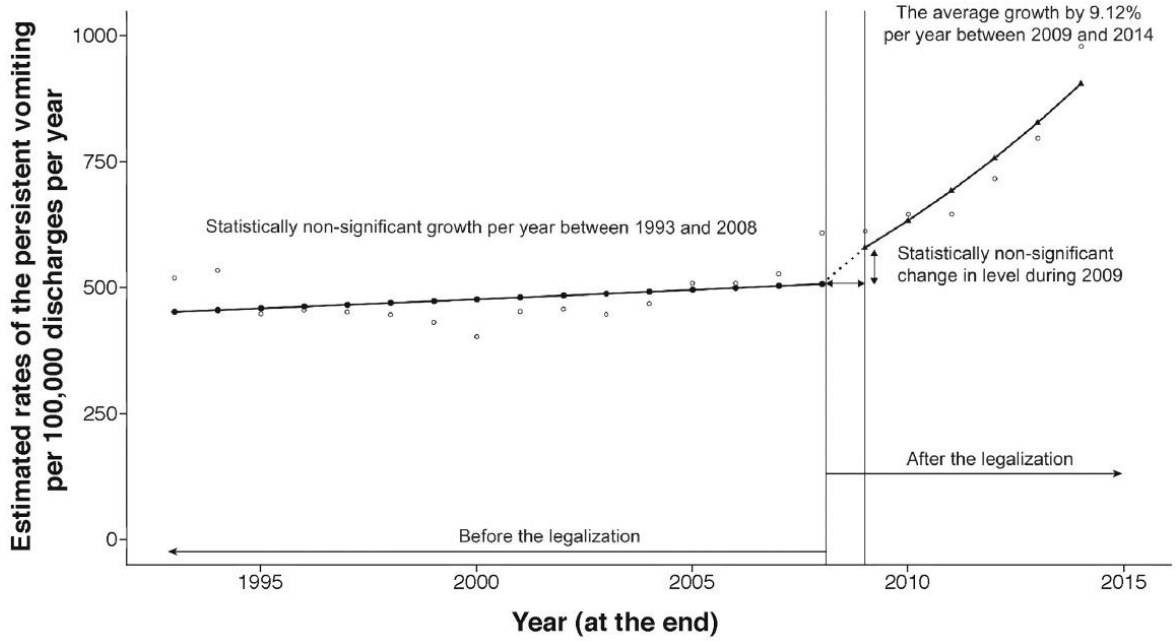


Kim HS, Anderson JD, Saghafi O, *et al*. Cyclic vomiting presentations following marijuana liberalization in Colorado. *Acad Emerg Med* 2015;22:694–699.

Trends in cannabis dependency and persistent vomiting in hospital admissions (HCUP data).



Note: white dots = observed rates; black dots and triangles = estimated rates; percentages and changes are statistically significant ($P < .05$) unless noted non-significant



Note: white dots = observed rates; black dots and triangles = estimated rates; percentages and changes are statistically significant ($P < .05$) unless noted non-significant

Al-Shammari M, Herrera K, Liu et al. Effects of the 2009 medical cannabinoid legalization policy on hospital use for cannabinoid dependency and persistent vomiting. *Clin Gastroenterol Hepatol* 2017 (online ahead of print)

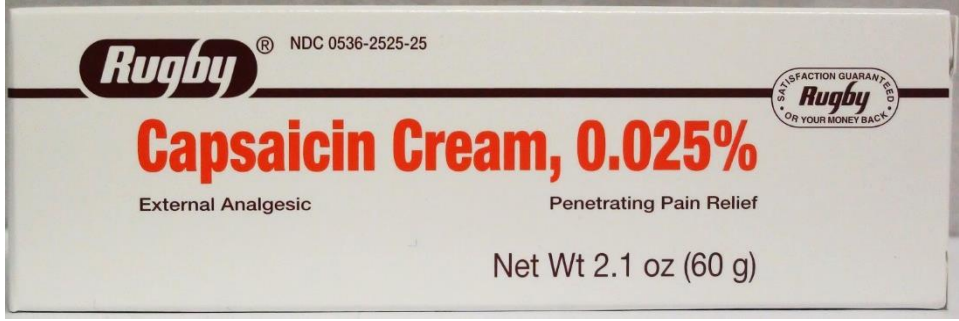
Clinical Gastroenterology and Hepatology

Treatment of CHS

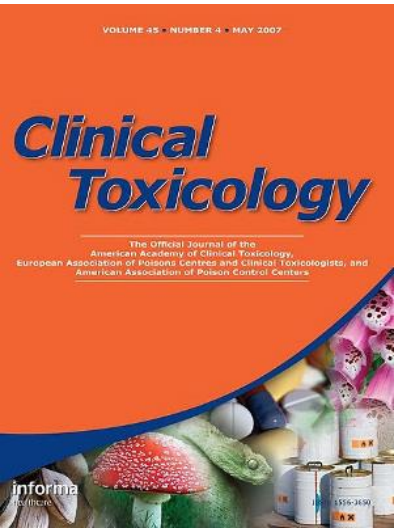
- Ondansetron – seldom effective
- Phenothiazines – somewhat more effective
- Opioids – somewhat helpful for pain, but not for nausea.
- IV fluids – often necessary to correct dehydration.

Witsil JC, Mycyk MB. Haloperidol, a Novel Treatment for Cannabinoid Hyperemesis Syndrome. *Am J Ther* 2017;24(1), e64–e67

Capsaicin



- TRPV-1 receptor agonist
- Often relieves symptoms when other treatments have failed.
- Mimics the effect of hot showers.
- Some patients dislike the burning sensation.



Dezieck L, Hafez Z, Conicella A, Blohm E, O'Connor MJ, Schwarz EJ, Mullins ME. Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: a case series. *Clin Toxicol* 2017;55:908-913.

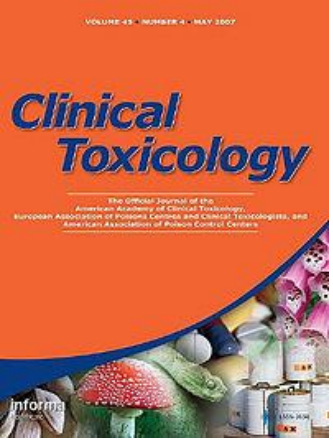
CHS Conclusions

- Cannabis Hyperemesis Syndrome is increasingly common.
- Unexplained abdominal pain, nausea, vomiting.
- Typically have negative workups.
- History of daily or nearly daily cannabis use.
- *Ask if hot showers give some relief*.

CHS Conclusions

- 5HT-3 antagonists are usually ineffective.
- High potency dopamine antagonists are somewhat more effective.
- Topical capsaicin is often effective.
- Symptoms will subside with abstinence.

Improving Treatment of Acetaminophen Poisoning with Acetylcysteine



CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 10, 924–1109
http://dx.doi.org/10.1080/15563650.2016.1245421

POISON Help
1-800-222-1222
AAPCC

NPDS REPORT 2015

2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report

James B. Mowry[a], Daniel A. Spyker[b,c], Daniel E. Brooks[d], Ashlea Zimmerman[e] and Jay L. Schauben[f]

2.168 M human exposure calls in 2015

- 106 K regarding APAP (5%)
  - 20,298 received IV acetylcysteine (22%)

BRITISH MEDICAL JOURNAL 3 NOVEMBER 1979 1097

PAPERS AND ORIGINALS

BMJ

Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning

L F PRESCOTT, R N ILLINGWORTH, J A J H CRITCHLEY, M J STEWART, R D ADAM, A T PROUDFOOT

British Medical Journal, 1979, **2**, 1097-1100

"Intravenous acetylcysteine was given in an initial dose of **150 mg/kg in 200 ml 5% dextrose over 15 minutes** followed by **50 mg/kg in 500 ml 5% dextrose over four hours** and **100 mg/kg in one litre 5% dextrose over the next 16 hours** (total dose 300 mg/kg in 20 hours). Roughly half of the patients were given Airbron, which is a 20% sterile aqueous solution of acetylcysteine for intrabronchial use. The remainder were given a similar solution specially prepared by the manufacturer for intravenous use."

Acetadote® PI follows the Prescott infusion recipe

Specifies a bag size that does NOT exist.

Uses NON-UNIT time intervals for 2nd & 3rd infusions.

Table 1. Three-Bag Method Dosage Guide by Weight, patients ≥ 40 kg

Body Weight		LOADING Dose 150 mg/kg in 200 mL diluent ◊ over 60 min	SECOND Dose 50 mg/kg in 500mL diluent over 4 hours	THIRD Dose 100 mg/kg in 1000mL diluent over 16 hours
(kg)	(lb)	Acetadote (mL)	Acetadote (mL)	Acetadote (mL)
100	220	75	25	50
90	198	67.5	22.5	45
80	176	60	20	40
70	154	52.5	17.5	35
60	132	45	15	30
50	110	37.5	12.5	25
40	88	30	10	20

Uses VOLUME instead of MASS units in preparation.

Two different concentrations which are unique to each patient.

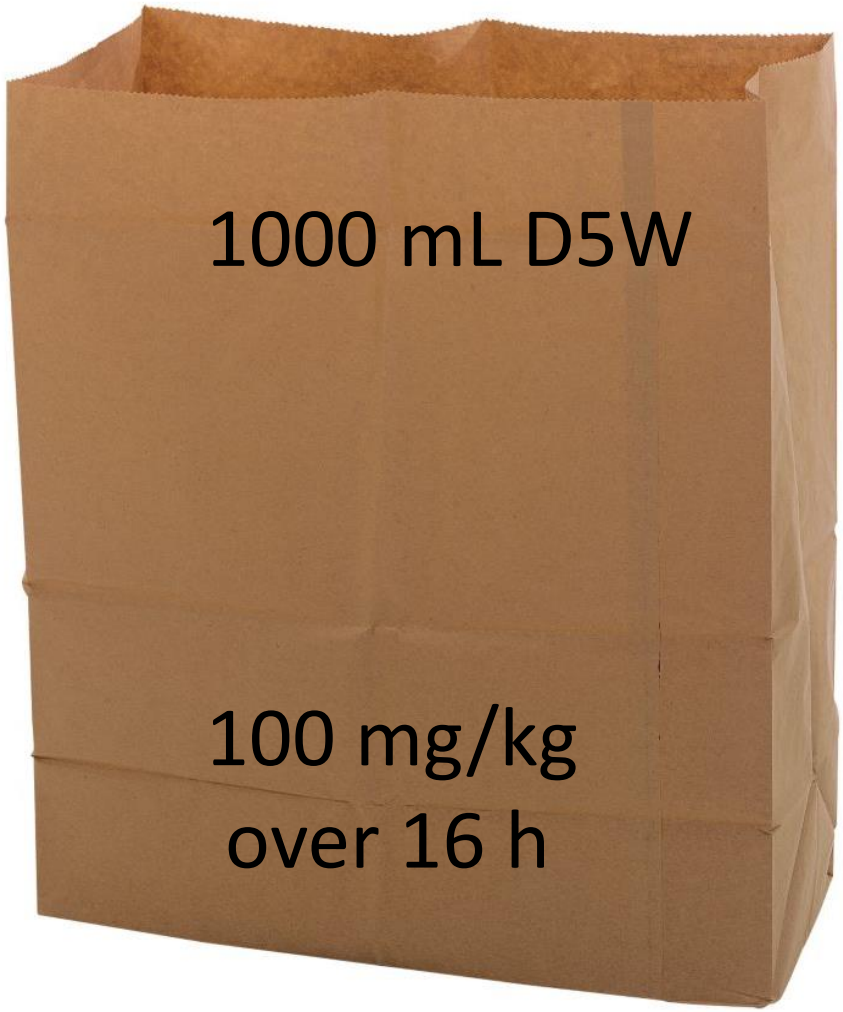
200 mL D5W

150 mg/kg over 1 h

500 mL D5W

50 mg/kg over 4 h

1000 mL D5W



100 mg/kg over 16 h

© ebas/AKM-GSI

BRITISH MEDICAL JOURNAL VOLUME 289 28 JULY 1984 217

PAPERS AND SHORT REPORTS

BMJ

Adverse reactions to acetylcysteine and effects of overdose

T G K MANT, J H TEMPOWSKI, G N VOLANS, J C C TALBOT

UK NPIS follow-up questionnaires sent to physicians who treated APAP ODs with IV Acetylcysteine from 1979 to 1983.

22 NAC overdoses with **five 10-fold overdoses**

- **2 died**.
- 3 survived after **hypotension (3), DIC (3), ARF (2).**

Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example

R. E. Ferner,[1] N. J. Langford,[1] C. Anton,[1] A. Hutchings,[2] D. N. Bateman[3] & P. A. Routledge[2]

[1]West Midlands Centre for Adverse Drug Reaction Reporting, City Hospital, Birmingham B18 7QH, [2]University of Wales College of Medicine Therapeutics and Toxicology Centre, Llandough Hospital, Cardiff CF64 2XX and [3]Scottish Poisons Information Bureau, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK

Measured NAC in 184 bags from 66 patients studied.

Only **37%** delivered +/- 10% of the intended dose.

17 bags (9%) from 10 patients deviated by **>50%** of the intended dose.

All 3 bags deviated **>50%** in 3 patients.

An assessment of the variation in the concentration of acetylcysteine in infusions for the treatment of paracetamol overdose

George P. Bailey[1,2*], David M. Wood[1,3], John R. H. Archer[1,3], Edmund Rab[4], Robert J. Flanagan[4,5] and Paul I. Dargan[1,3]

BACKGROUND

Intravenous acetylcysteine is the treatment of choice for paracetamol poisoning. A previous UK study in 2001 found that 39% of measured acetylcysteine infusion concentrations differed by >20% from anticipated concentrations. In 2012, the UK Commission on Human Medicines made recommendations for the management of paracetamol overdose, including provision of weight-based acetylcysteine dosing tables. The aim of this study was to assess variation in acetylcysteine concentrations in administered infusions following the introduction of this guidance.

METHODS

A 6-month single-centre prospective study was undertaken at a UK teaching hospital. After preparation, 5-ml samples were taken from the first, second and third/any subsequent acetylcysteine infusions. Acetylcysteine was measured in diluted (1:50) samples by high-performance liquid chromatography. Comparisons between *measured* and *expected* concentrations based on prescribed weight-based dose and volume were made for each infusion.

RESULTS

Ninety samples were collected. There was a variation of ≤10% in measured compared to expected concentration for 45 (50%) infusions, of 10–20% for 27 (30%) infusions, 20.1–50% for 14 (16%) infusions and >50% for four (4%) infusions. There was a median (interquartile range) variation in measured compared to expected concentration of −3.6 mg ml^{-1} (−6.7 to −2.3) for the first infusion, +0.2 mg ml^{-1} (−0.9 to +0.4) for the second infusion and −0.3 mg ml^{-1} (−0.6 to +0.2) for third and fourth infusions.

CONCLUSION

There has been a moderate improvement in the variation in acetylcysteine dose administered by infusion. Further work is required to understand the continuing variation and consideration should be given to simplification of acetylcysteine regimes to decrease the risk of administration errors.

Br J Clin Pharmacol (2017) **83** 393–399

Dose was accurate to within 10% only 50% of the time.


IN GOD
1964

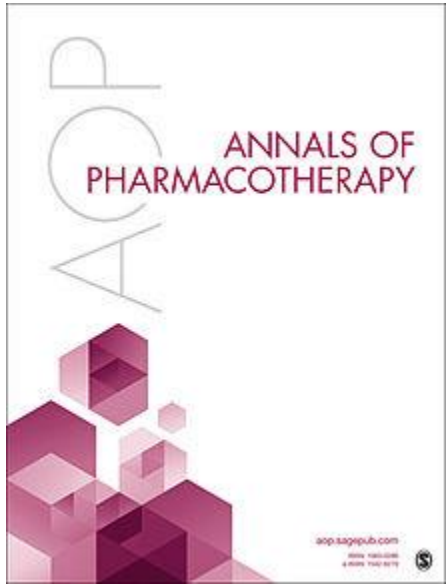

SEX PANTHER
ANCHORMAN'S
SEX
PANTHER
ANCHORMAN'S
SEX PANTHER


60% of the time
it works every time
Celebremix

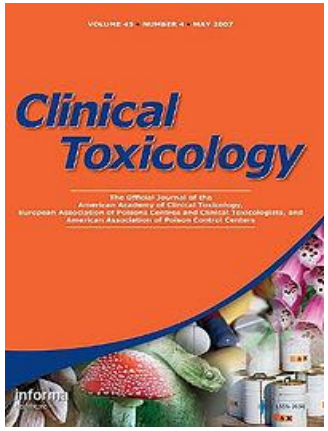
Acetaminophen Overdose Treatment Errors

Retrospective review of **221** acetaminophen overdose cases treated with IV acetylcysteine.

- **84** medication errors occurred in **74 (33%)** patients.
  - **1.4% incorrect dose**
  - **5% incorrect infusion rate**,
  - **18.6% >1 hour of interruption** in therapy
  - 13.1% unnecessary administration



Hayes BD, Klein-Schwarz W, Doyon S. Frequency of medication errors with intravenous acetylcysteine for acetaminophen overdose. *Ann Pharmacother*. 2008;42(6):766–770.



Clinical Toxicology (2011), **49**, 755–759
Copyright © 2011 Informa Healthcare USA, Inc.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2011.609821

BRIEF COMMUNICATION

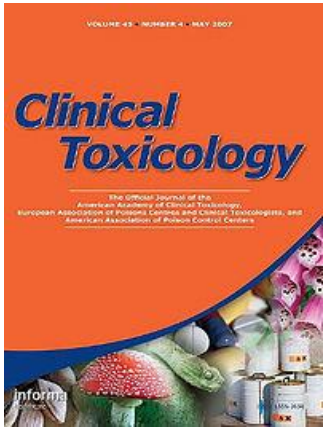
Hemolysis and Hemolytic Uremic Syndrome following Five-fold N-Acetylcysteine Overdose

Grams instead of mL

MICHAEL E. MULLINS and IRENA V. VITKOVITSKY

Washington University, Emergency Medicine, 660 S Euclid Avenue, Campus Box 8072, St. Louis, 63110 United States

Context. Intravenous acetylcysteine (Acetadote™ in the US) is the treatment of choice for acute acetaminophen poisoning in most of the world. However, the complicated dosing regimen is prone to errors in preparation and administration. *Case report.* A 21 year-old woman (70 kg) took an overdose of acetaminophen and ethanol. Her serum acetaminophen concentration was > 200 mg/L. Acetylcysteine infusion was ordered. Due to misreading of the columns in the table in the Acetadote™ package insert, she received a five-fold overdose of 52.5 g of acetylcysteine in 500 mL over 1 h and then 17.5 g of acetylcysteine in 500 mL to run over 4 h. The dose error was detected 20 min into the second infusion. Her acetaminophen concentration fell quickly, and her highest transaminase concentrations occurred day 2. Her hemoglobin and hematocrit quickly dropped from 14.8 g/dL and 44.0% on admission to 6.2 g/dL and 17.3% on day 7. Subsequently she developed hematuria and a rapidly rising serum creatinine. She was transferred to a tertiary care hospital, where she underwent hemodialysis every two days for two weeks, transfusions of packed red blood cells, and plasmapheresis until hematologic testing ruled out thrombotic thrombocytopenia purpura. *Discussion.* A five-fold overdose of acetylcysteine was followed by unexpected hemolysis and acute renal failure. The mechanism of hemolysis after acetylcysteine overdose is unclear. A simpler infusion regimen with standard concentrations would prevent a similar error.



Clinical Toxicology (2011), **49**, 423–425
Copyright © 2011 Informa Healthcare USA, Inc.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2011.583664

BRIEF REPORT

Massive acetylcysteine overdose associated with cerebral edema and seizures

KENNON HEARD and TAMMI H. SCHAEFFER

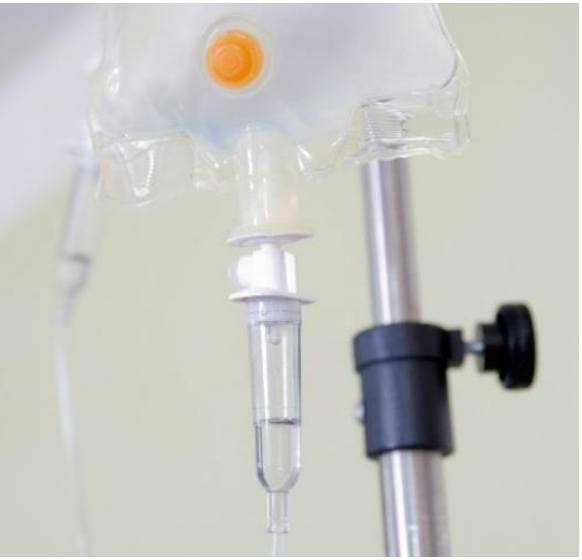
Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO, USA, and Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Context. Acetylcysteine is a safe and effective treatment for the prevention of hepatic injury due to acetaminophen poisoning. While dosing errors are common, in most cases, overdoses produce minimal clinical effects. *Case report*. We describe a patient who received 150 g of IV acetylcysteine over 32 h when the clinician ordered the infusion doses be administered as an hourly dose (100 mg/kg/h) rather than administered over the infusion duration (100 mg/kg over 16 h). After approximately 28 h of receiving 100 mg/kg/h, the patient developed delirium, and seizures that progressed to cerebral edema, uncal herniation, and ultimately severe brain injury. No other cause for her symptoms was identified during an extensive workup. *Discussion*. This case suggests that massive IV acetylcysteine overdose can cause cerebral dysfunction and life-threatening effects.

Keywords Acetylcysteine; Overdose; Acetaminophen

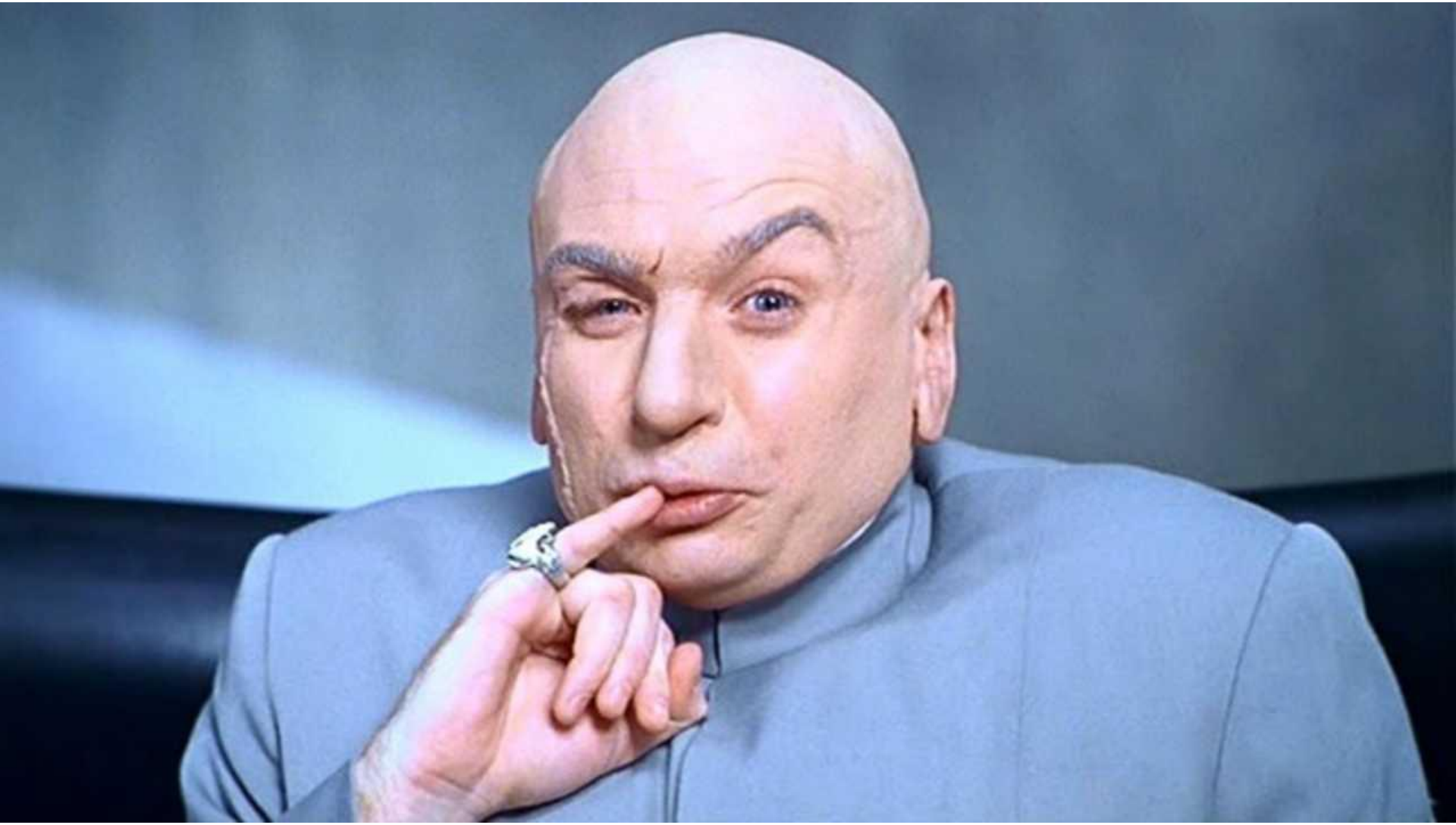
mg/kg/h instead of mg/kg/16h

Remember the Rule of 6?



- 6 mg/kg dopamine added to 100 mL
  - 1 mL/h = 1 mcg/kg/min
- 0.06 mg/kg epinephrine added to 100 mL
  - 1 mL/h = 0.01 mcg/kg/min

McLeroy PA. The rule of six: Calculating intravenous infusions in a pediatric crisis situation. *Hosp Pharm* 1994;29(10):939-40, 943.



Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

ISMP Quarterly Action Agenda April-June 1999.

Avoid Preparing Infusions Using the Rule of 6 or Broselow Tape. *ISMP Medication Safety Alert*. 2005;10(4).

The Joint Commission

NPSG 2004

Goal 3.b. ***Drug concentrations should be limited to reduce the potential for error*** associated with stocking various concentrations of the same drug.

IV Acetylcysteine at BJH and SLCH

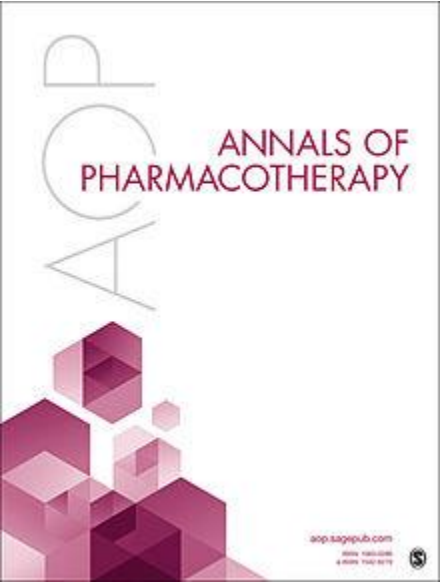
30 grams of Acetylcysteine in **1 L** of D5W.

Standard concentration: **30 mg/mL**.

If Pt Wt </= 40 kg, then 15 grams in 500 mL of D5W. (30 mg/mL)

IV Acetylcysteine at BJH and SLCH

- Loading dose: **150 mg/kg/h for 1 hour**
- Maintenance infusion: **12.5 mg/kg/h** (equal to rate in middle bag of three bag method)
- Recheck APAP, AST, ALT at 20-24 h from ingestion (if known) to decide whether to stop or continue.



Evaluation of a Simplified *N*-Acetylcysteine Dosing Regimen for the Treatment of Acetaminophen Toxicity

Michael T Johnson, Craig A McCammon, Michael E Mullins, and S Eliza Halcomb

Table 3. Comparison of FDA and Institutional Protocol[a]

	FDA Protocol (n = 5)	Institutional Protocol (n = 65)
Pts. with ≥1 errors	3 (60%)	25 (38%)
Pts. with no errors	2 (40%)	40 (62%)

FDA = Food and Drug Administration.
[a]p = 0.383, Fisher exact test. Risk estimate: OR = 1.53; 95% CI 0.52 to 4.57.

- Fewer errors with one-bag method.
- Compared to Maryland PCC data (using same definitions), total error rate was **20% at BJH** compared to **38% from Maryland PCC**.
- Administration errors dropped from **25% to 9%**.

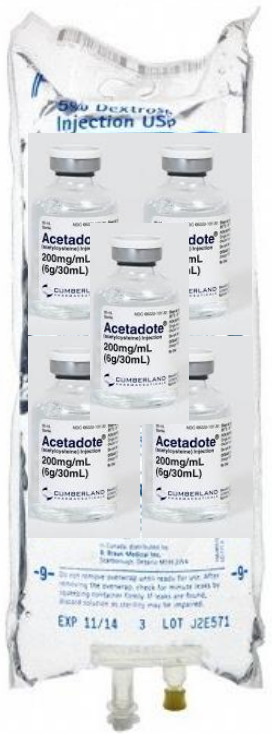
Bag 1
150 mg/kg of solution
0.75mg/kg/mL= 60 mg/mL for 80 kg patient

Total dose = 300 mg/kg over 21 h

Bag 2
50 mg/kg of solution with
0.1 mg/kg/mL=8 mg/mL for
80 kg patient

Bag 3
100 mg/kg of solution with
0.1 mg/kg/mL = 8 mg/mL for 80 kg patient.

Loading infusion rate
150 mg/kg/h x 1 h



Total dose = 400 mg/kg over 21 h

Maintenance infusion
12.5 mg/kg/h x 20 h

0 1 5 Hours 21

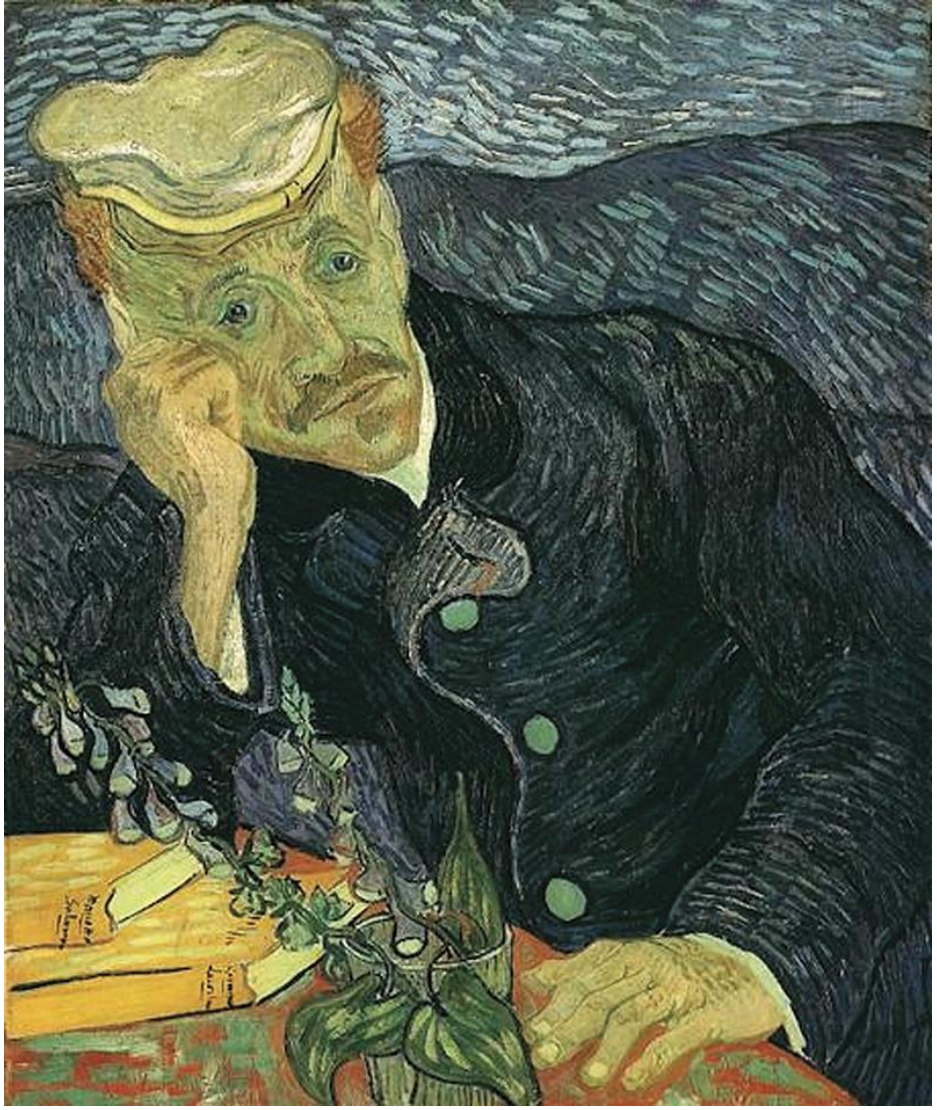
Standard concentration, easier to prepare, easier to administer, fewer errors, well tolerated

30 grams of Acetylcysteine in 1 L D5W.

Standard concentration:
30 mg/mL

Loading dose:
150 mg/kg/h for 1 h

Maintenance infusion:
12.5 mg/kg/h until patient meets stopping criteria.



Portrait of Dr Gachet (1890) by Vincent van Gogh

Digoxin

- Rates of ED visit and hospital admission remain steady (NIESS and NAMCS data) at estimated >5,000 per year in US.

- 2015 NPDS data: 616 uses of Fab out of 1916 digoxin or 1409 cardiac glycoside plant exposures.

See I, Shehab N, Kegler SR, et al. Emergency Department Visits and Hospitalizations for Digoxin Toxicity, United States, 2005 to 2010. *Circ Heart Fail* 2014;7:28-34.

Mowry JB, Spyker, DA Brooks DE, et al. 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report, *Clini Toxicol* 2016 54:10, 924-1109.

Antidote: When? How much?

- Elevated [K+] ?
- Elevated [digoxin] ?
- Digoxin dose?
- EKG changes?
- Other symptoms?

Fab antidote manufacturer's recommendations

Clinical Conditions	Dosage
Acute ingestion of unknown amounts of digoxin and toxicity in the absence of a serum digitalis concentration or estimated ingestion amount	Administer 20 vials of DigiFab®. Monitor for volume overload in small (< 20 Kg) children. Start with 10 vials followed by an additional 10 vials, if needed, to avoid a febrile reaction.
Chronic digoxin toxicity in the absence of a serum digitalis concentration	Administer 6 vials of DigiFab® in Adults and Children ≥ 20 Kg. Administer 1 vial of DigiFab® in Infants and Children < 20 Kg.
Acute ingestion of known amounts of digoxin	Dose (in vials) = $\frac{\text{Amount of digoxin ingested (in mg)}}{\text{0.5 mg/vial}}$
Chronic digoxin toxicity and known serum digitalis concentration	Dose (in vials) = $\frac{\text{(Serum digoxin ng/mL)(weight in kg)}}{100}$


Leaving Brooklyn
Fuhgeddaboudit
Marty Markowitz
Borough President
Michael R. Bloomberg
Mayor

CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 6, 488–494
http://dx.doi.org/10.1080/15563650.2016.1175620

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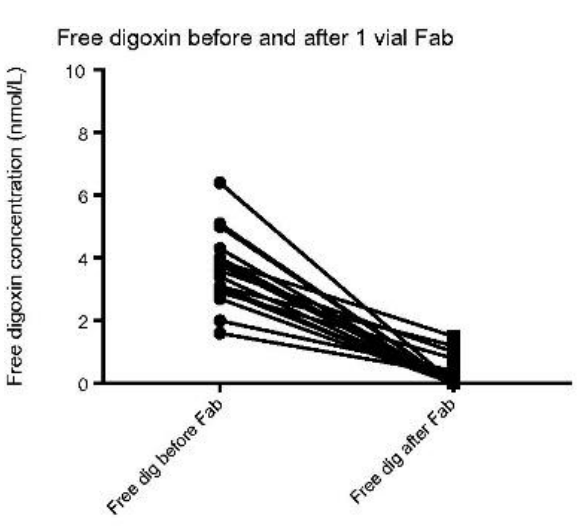
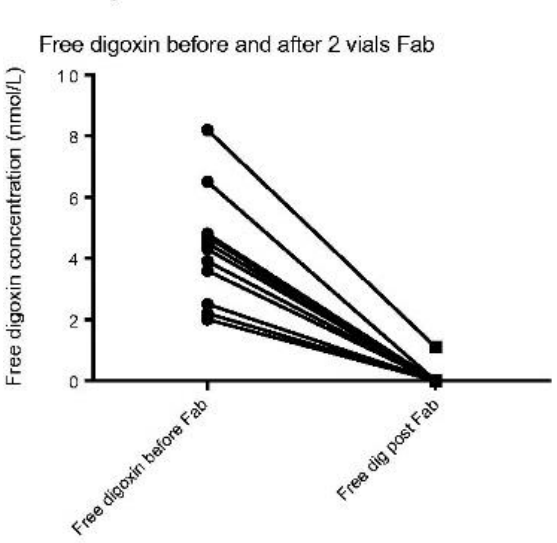
CLINICAL RESEARCH

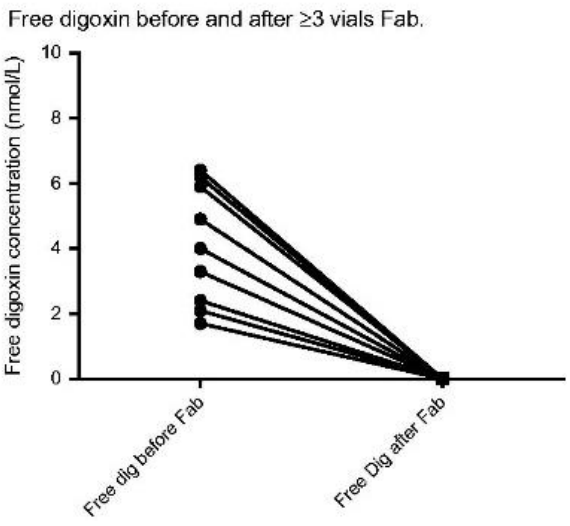
Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1)

Betty S. Chan[a,b], Geoffrey K. Isbister[b,c,d], Margaret O'Leary[c,d], Angela Chiew[a,b] and Nicholas A. Buckley[b,e]

[a]Clinical Toxicology Unit and Emergency Department, Prince of Wales Hospital, Sydney, New South Wales, Australia; [b]New South Wales Poisons Information Centre, Sydney Children's Hospital at Westmead, Sydney, New South Wales, Australia; [c]Clinical Toxicology Research Group, University of Newcastle, Newcastle, Australia; [d]Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, Newcastle, Australia; [e]Department of Clinical Pharmacology, University of Sydney, Sydney, New South Wales, Australia







Revised recommendations

Acute Intoxication

- Give 80 mg (2 vials) digoxin immune Fab, repeated as required according to clinical parameters because the onset of clinical response is usually rapid (i.e. 60 minutes).

Chronic Intoxication

- Give 40 mg (1 vial) digoxin immune Fab at a time and repeat after 60 minutes if patient is still symptomatic, sooner if patient is clinically unstable.
- In general, 40-120mg (1-3 vials) should be sufficient.

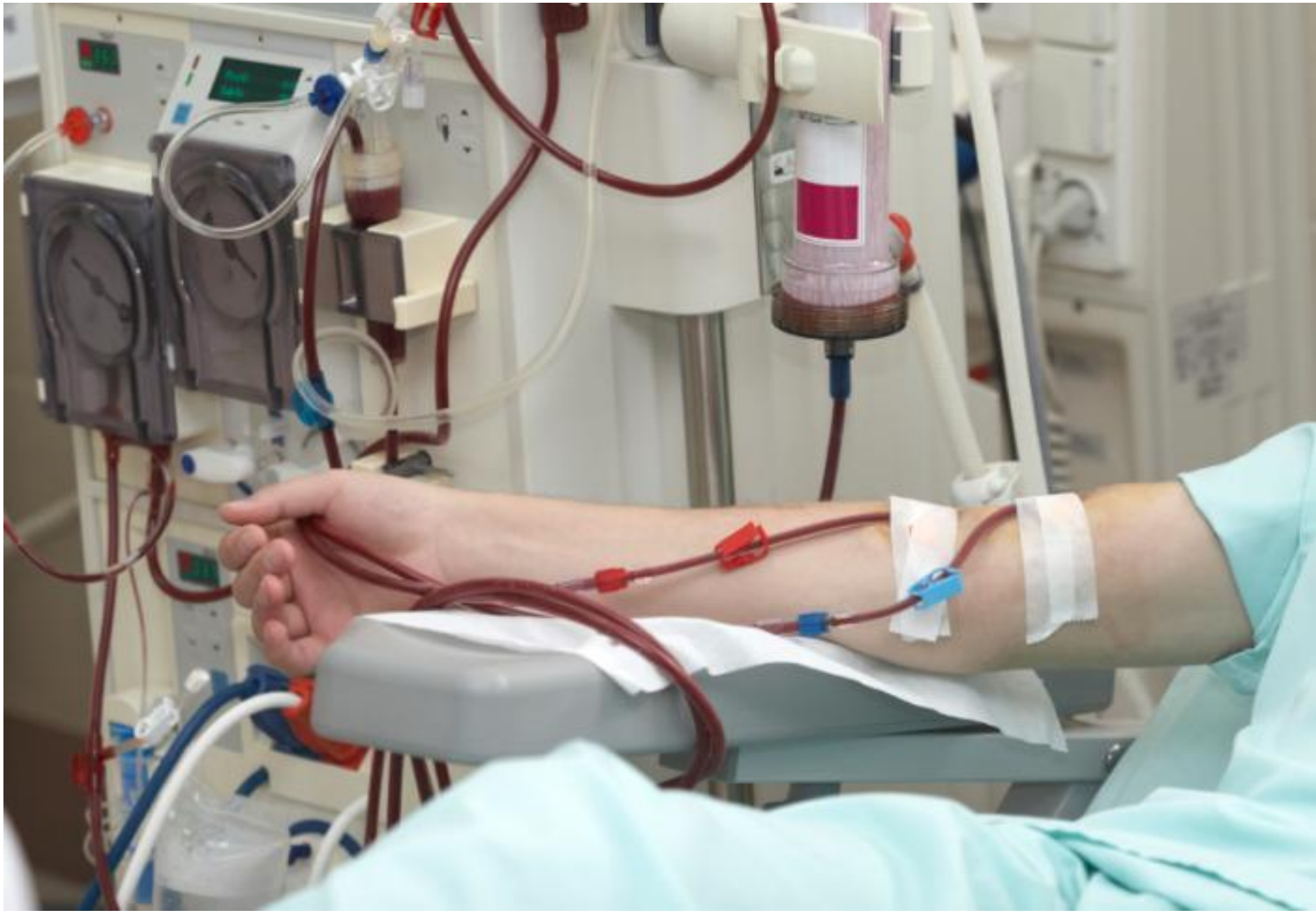


Table 3. Indications for extracorporeal treatment in the treatment of lithium poisoning

Indication for ECTR	Goldfrank's *Toxicologic Emergencies*, 9th Ed. (216)	EMedicine (emedicine.medscape.com) (215)	Toxbase (toxbase.org) (214)	Toxinz (toxinz.com) (213)	Olson's *Poisoning and Drug Overdose*, 6th Ed. (212)	UpToDate (uptodate.com) (211)	Murray's *Toxicology Handbook*, 2nd Ed. (210)
Absolute $[Li^+]$ regardless of symptoms (mEq/L)	≥4	≥4	≥7.5			>4	
$[Li^+]$ in chronic exposure (mEq/L)	≥2.5	≥2.5	>4	>4		>2.5	>2.5
Symptoms/signs	Neurotoxicity, kidney impairment	Neurotoxicity	Neurotoxicity	Neurotoxicity	Seizures or impaired mental status, kidney impairment	Significant toxicity, kidney impairment	Neurotoxicity

ECTR, extracorporeal treatment. Modified from reference 28, with permission.

Decker et al. Blood Purification for Lithium Poisoning. *Clin J Am Soc Nephrol* 2015;10: 875–887

Quarterly Journal of Medicine, New Series XLVII, No. 186, pp. 123–144, April 1978

QJM

Lithium Intoxication

(REPORT OF 23 CASES AND REVIEW OF 100 CASES FROM THE LITERATURE)

HANS ERIK HANSEN* AND AMDI AMDISEN**

From the Department of Medicine C, Aarhus Kommunehospital and Aarhus University Psychiatric Institute, Psychopharmacology Research Unit**, Psychiatric Hospital in Aarhus.*

Graded Li+ intoxications as Grade I, II, or III.

No methods to describe classification.

Therapeutic Drug Monitoring
22:650–655 © 2000 Lippincott Williams & Wilkins, Inc., Philadelphia

Lithium Poisoning From a Poison Control Center Perspective

Benoit Bailey* and Michael McGuigan†

**Divisions of Clinical Pharmacology and Toxicology and of Emergency Medicine, Department of Pediatrics, Hôpital Ste-Justine, Montréal, Québec, Canada; †Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, The Hospital for Sick Children and The Ontario Regional Poison Information Centre, Toronto, Ontario, Canada*

207 Li+ cases in Ontario, Canada.
Referred to Hansen & Amdisen “criteria” but unable to reproduce the classification consistently.

Recommended HD based upon [Li+] > 4.0 mmol/L (acute) or > 2.5 mmol (chronic) or severe symptoms.

Therapeutic Drug Monitoring
22:650–655 © 2000 Lippincott Williams & Wilkins, Inc., Philadelphia

Lithium Poisoning From a Poison Control Center Perspective

Benoit Bailey* and Michael McGuigan†

**Divisions of Clinical Pharmacology and Toxicology and of Emergency Medicine, Department of Pediatrics, Hôpital Ste-Justine, Montréal, Québec, Canada; †Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, The Hospital for Sick Children and The Ontario Regional Poison Information Centre, Toronto, Ontario, Canada*

12 acute, 0 recommended for HD, 0 underwent HD (no discordant cases)

174 A/C, 9 recommended for HD, done in 6 (3 discordant cases)

1 death despite HD (peak Li+ 8.9 mmol/L) due to aspiration

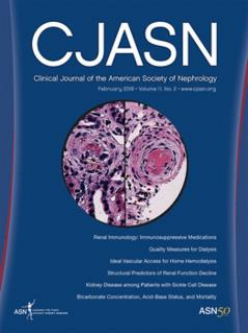
19 chronic,

8 recommended for HD, done in 2 (6 discordant cases)

1 death in patient with HD

11 not recommended for HD, 1 dialyzed (discordant case)

No apparent Δ in Pts with HD and Pts not dialyzed despite recommendation for HD.



Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup

THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP

Brian S. Decker, David S. Goldfarb, Paul I. Dargan, Marjorie Friesen, Sophie Gosselin, Robert S. Hoffman, Valéry Lavergne, Thomas D. Nolin, and Marc Ghannoum on behalf of the EXTRIP Workgroup

ECTR *recommended* if any of the following conditions are present (1D):

(1) If kidney function is impaired and the [Li+] is >4.0 mEq/L.

(2) In the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias, irrespective of the [Li+].

ECTR *suggested* if any of the following conditions are present (2D):

(3) If [Li+] is >5.0 mEq/L.

(4) If significant confusion is present.

(5) If the expected time to reduce [Li+] to <1.0 mEq/L with optimal management is >36 hours.

Decker et al. Blood Purification for Lithium Poisoning. *Clin J Am Soc Nephrol* 2015;10: 875–887

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VOL. 54, NO. 8, 615–623
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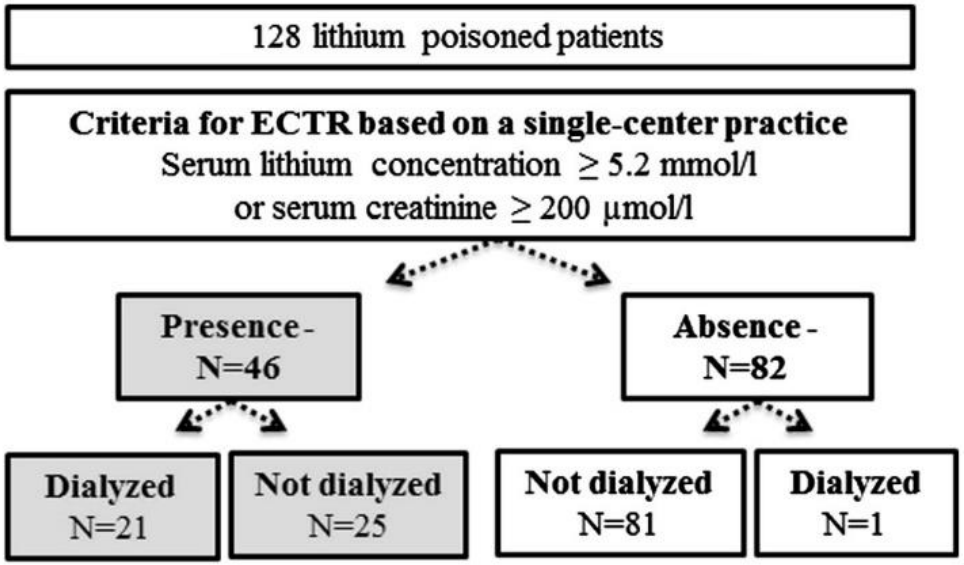
CLINICAL RESEARCH

Lithium poisoning in the intensive care unit: predictive factors of severity and indications for extracorporeal toxin removal to improve outcome

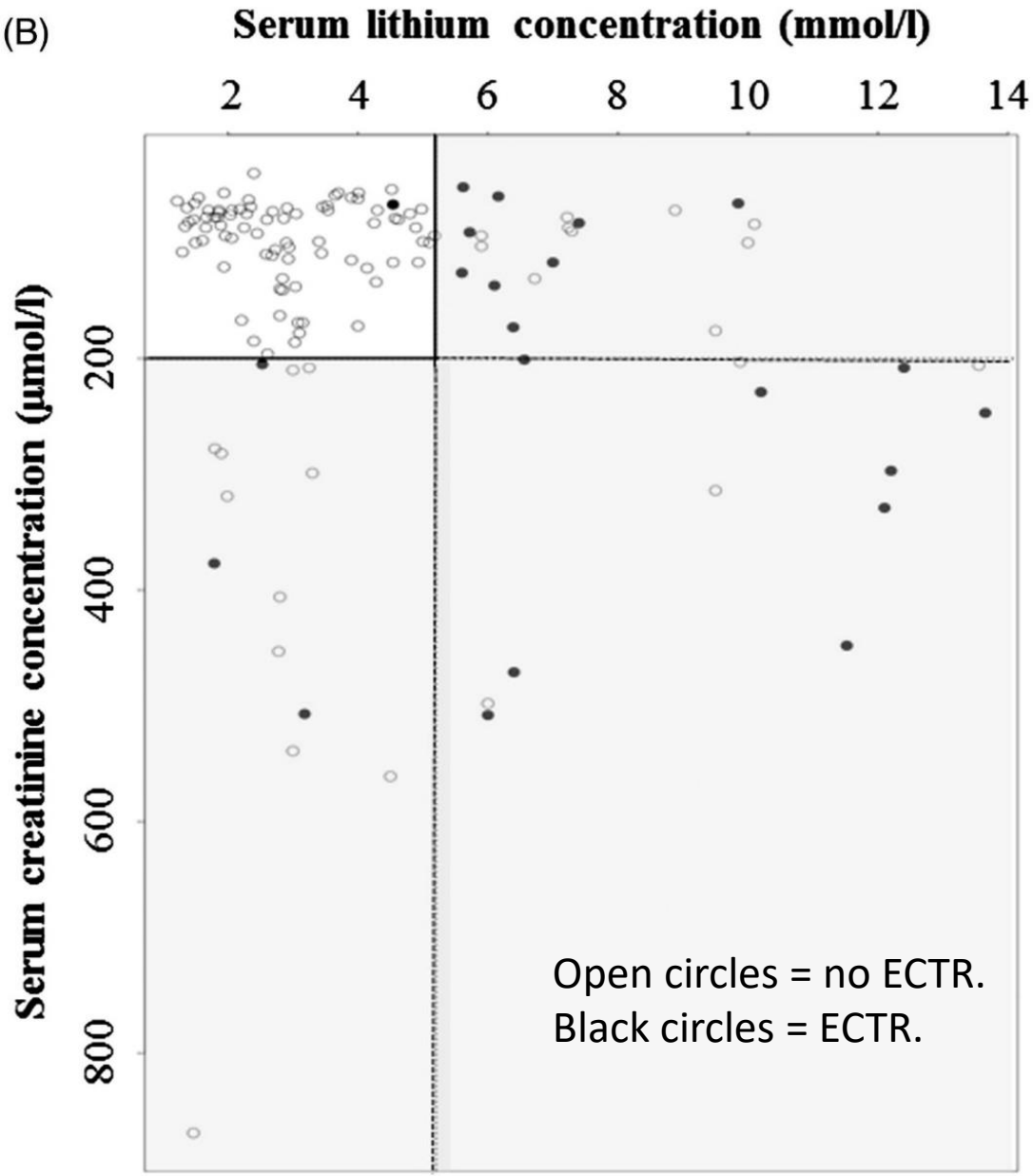
Dominique Vodovar[a,b,c,d], Souleiman El Balkhi[b,c,d,e], Emmanuel Curis[b,c,d], Nicolas Deye[a,b] and Bruno Mégarbane[a,b,c,d]

[a]Department of Medical and Toxicological Critical Care, Assistance Publique - Hôpitaux de Paris, Lariboisière Hospital, Paris, France; [b]Paris-Diderot University, Paris, France; [c]Research Unit 1144, Institut National de la santé et de la recherche médicale (INSERM), Paris, France; [d]Paris-Descartes University, Paris, France; [e]Toxicology Laboratory, Assistance Publique - Hôpitaux de Paris, Lariboisière Hospital, Paris, France

(A)



Death (N,%)	1 (5)	3 (12)	0 (0)	0
Neurologic impairments (N,%)	3 (15)*	12 (54)*	9 (11)	0
ICU stay (days)	14.0 [7.2-21.0]	9.0 [6.0-20.5]	4.0 [2.0-6.5]	3



Vodovar D, et al. Lithium poisoning in the intensive care unit: predictive factors of severity and indications for extracorporeal toxin removal to improve outcome. *Clin Toxicol* 2016;54:615-623.

Toxic takeaways

- SGLT-1/2 inhibitors risk ketoacidosis despite near normal glucose concentrations.
- DPP-4 inhibitors may increase risk of angioedema during co-administration with ACE inhibitors.
- Cannabis Hyperemesis may occur with long-term, frequent cannabis abuse. Relief with hot showers may be a clue. Topical capsaicin or potent IV dopamine antagonists are helpful.
- Standard concentration N-Acetylcysteine of 30 mg/mL improves dose consistency and accuracy.
- Low doses of Digoxin Fab are best in digoxin poisoning.
- Higher threshold for dialysis in Lithium poisoning may be better.