pshp ANNUAL ASSEMBLY

BRIDGING THE FUTURE OF PHARMACY 2022

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2022 Updates in Clinical Pharmacy Practice

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Disclosures

- The presenters have nothing to disclose.

Objectives

- Discuss three antiepileptic drugs recently approved
- Review strategies for the treatment of acute agitation in the emergency department
- Review updated literature for the management of patients with septic shock regarding volume of fluid resuscitation and use of IV vitamin C

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What's new in antiepileptic drugs

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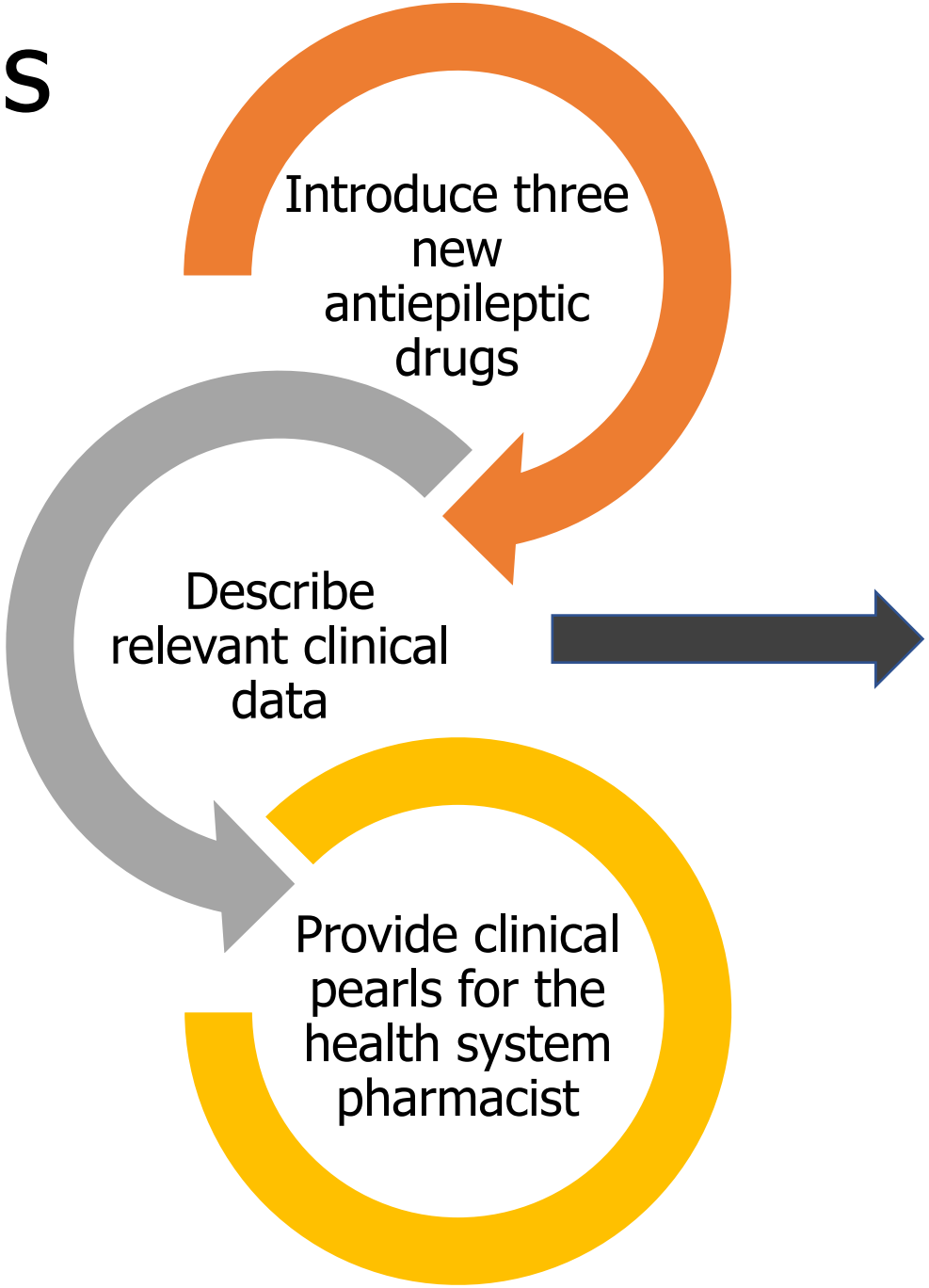
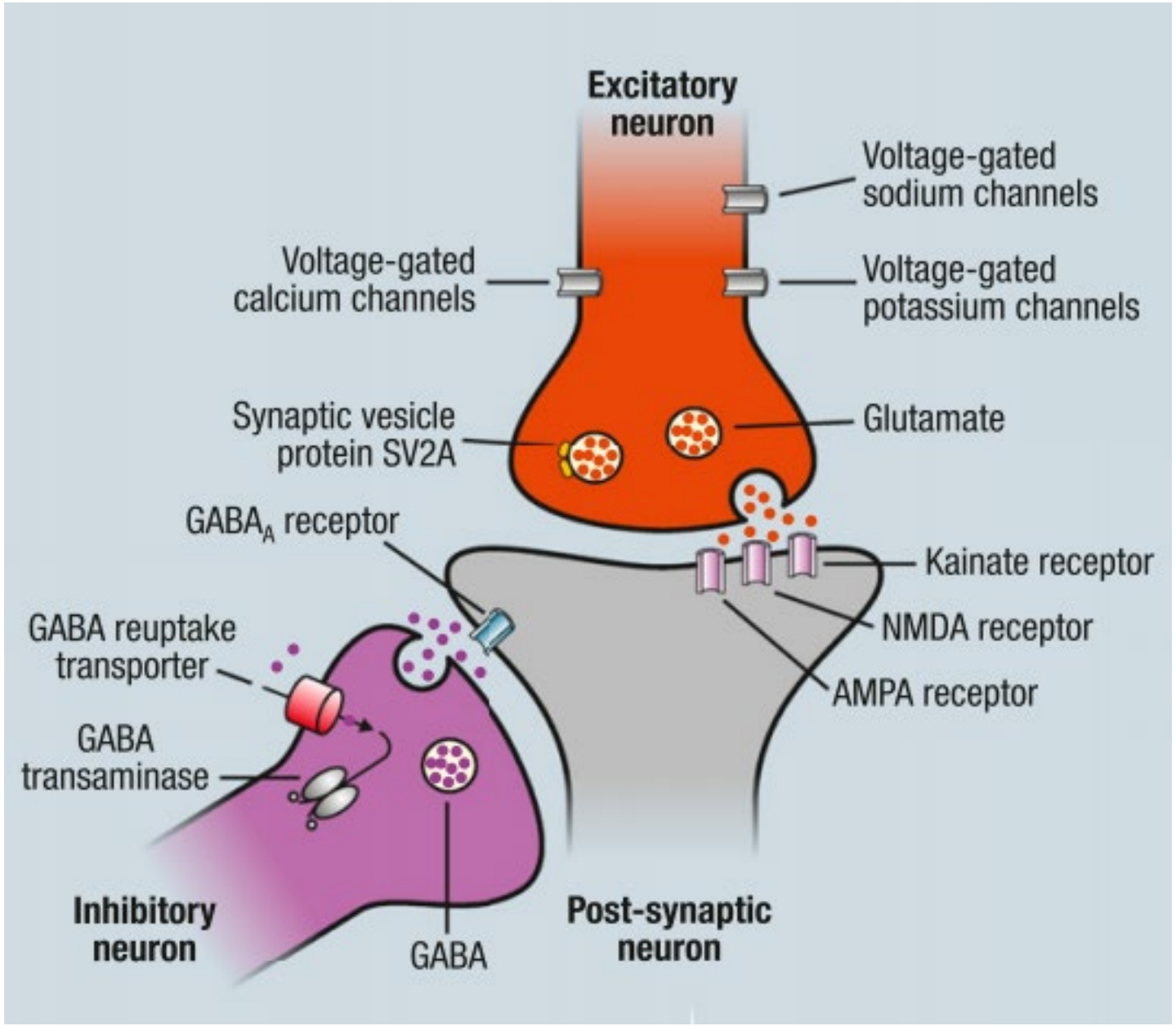
Objectives



- Cenobamate
- Cannabidiol
- Fenfluramine



Pharmacol Rev. 2016;68(3):563-602.

Cenobamate (XCOPRI®)

- U.S. approval: 2019
- C-V
- FDA approved indication: for the treatment of partial-onset seizures in adult patients
  - Has not been studied as monotherapy; should be reserved as adjunctive therapy for treatment-resistant seizures
- Mechanism of action: inhibits voltage-gated sodium channels and modulates $GABA_A$ receptors (at non-benzodiazepine sites)

CNS Drugs. 2020;34:1105-20. Annals of Pharmacotherapy. 2021;55(3):318-29.
XCOPRI (cenobamate) [package insert]. Paramus, NJ: SK Life Science, Inc.; 2020.

Clinical Trial Data

- From 2 Phase II randomized, double-blind, placebo controlled clinical trials

Table 2. Characteristics of important clinical trials of cenobamate.[28,29]

	NCT01397968		NCT01866111			
PARAMETER	CNB200	PL	CNB100	CNB200	CNB400	PL
No. of patients	113	109	108	110	111	108
No. of females	58	51	51	56	59	50
Change in seizure frequency (%)	-55.6***	-21.5	-35.5**	-55***	-55***	-24
≥50% seizure responder rate (%)	50.4***	22.2	40*	56***	64***	25
Incidence of TRAEs (%)	59.3	45.9	57	65	83	43
Incidence of SAEs (%)	1.8	3.7	9	4	7	6
Drug discontinuation rate (%)	4.4	2.8	11	15	22	5

Dosages for CNB are mg per day. Results are presented as median changes from baseline where applicable.
CNB, cenobamate; PL, placebo; TRAEs, treatment-related adverse events; SAEs, serious adverse events.
*$P \leq .03$, ** $P = .007$, *** $P \leq .0001$ vs placebo.

J Cent Nerv Syst Dis. 2022;14:1-5. Neurology. 2020:94(22):e2311-22. Lancet Neurol. 2020;19(1):38-48.

Cenobamate Safety

- Common ADRs

Outcome	Number of studies [References]	Number of events/participants (%)		I^2 (%)	Risk ratio (99% CI)	p Value
		CNB	Placebo			
Any AE	2 [26, 27]	340/442 (76.9)	115/217 (53.0)	0.0	1.14 (0.99–1.31)	0.021
Treatment-related AE	2 [26, 27]	293/442 (66.3)	96/217 (44.2)	37.2	1.46 (1.17–1.83)	<0.001
Any SAE	2 [26, 27]	24/442 (5.4)	10/217 (4.6)	0.0	0.99 (0.36–2.75)	0.978
Somnolence	2 [26, 27]	109/442 (24.7)	22/217 (10.1)	16.7	2.35 (1.31–4.24)	<0.001
Dizziness	2 [26, 27]	103/442 (23.3)	33/217 (15.2)	0.0	1.53 (0.94–2.49)	0.026
Headache	2 [26, 27]	49/442 (11.1)	20/217 (9.2)	34.5	1.27 (0.63–2.57)	0.374
Nausea	2 [26, 27]	31/442 (7.0)	6/217 (2.8)	0.0	2.98 (0.92–9.61)	0.017
Fatigue	2 [26, 27]	71/442 (16.1)	16/217 (7.4)	0.0	1.96 (0.97–3.95)	0.014
Nystagmus	2 [26, 27]	25/442 (5.7)	1/217 (0.5)	0.0	7.83 (0.91–67.64)	0.014

- Serious ADRs

QT shortening

- dose dependent
- higher % in cenobamate group had QT shortening of >20 msec compared to placebo

DRESS

(drug reaction with eosinophilia and systemic symptoms)

- 3 cases, including 1 fatality when titrated rapidly
- no cases reported using recommended slow titration

Epilepsia. 2020;61:1099–1108. CNS Drugs. 2020;34:1105-20.

Cenobamate Dosing

Maximum dosage: If needed based on clinical response and tolerability, **dosage may be increased above 200 mg/day by increments of 50 mg/day every 2 weeks to a maximum of 400 mg/day.**

XCOPRI may be taken any time with or without food. Swallow tablets whole with liquid. Do not crush or chew.

For patients with mild or moderate hepatic impairment, the maximum recommended dosage is 200 mg once daily.

- Once daily dosing (half life ~30-76 hours)
- Should not be chewed or crushed
  - soluble in aqueous solutions

XCOPRI (cenobamate) [package insert]. Paramus, NJ: SK Life Science, Inc.; 2020.

Cenobamate Clinical Pearls

- Drug interactions
  - hepatically metabolized
  - inhibits CYP2C19
  - induces CYP2B6 and CYP3A4
- Monitoring
  - liver function tests
  - EKG
  - potassium

Table 2. Cenobamate Potential Drug Interactions.[13,16,17,19,20]

Drug/Substrate	Effect	Evidence	Dosing considerations
Lamotrigine	Decreased lamotrigine concentrations	Based on population pharmacokinetic analyses, lamotrigine concentrations are expected to decrease by 21%-52%	Increased doses of lamotrigine will likely be necessary
Levetiracetam	Decreased levetiracetam concentrations	Based on population pharmacokinetic analyses, levetiracetam concentrations are expected to decrease by 4%-13%	Although reduction in concentrations of levetiracetam may not be clinically meaningful, patients should be monitored to determine if a dose increase is necessary
Carbamazepine	Decreased carbamazepine concentrations	In patients taking carbamazepine and cenobamate, carbamazepine demonstrated a decrease in AUC of 24%	Increased doses and monitoring of carbamazepine will likely be necessary
Phenobarbital	Decreased cenobamate concentrations and increased phenobarbital concentrations	In patients taking phenobarbital and cenobamate, phenobarbital demonstrated an increase in AUC of 37% and C_{max} of 34%. The AUC of cenobamate was decreased by 15%	Phenobarbital will likely need a dose reduction when administered with cenobamate. Increased monitoring will likely be needed
Phenytoin	Decreased cenobamate concentrations and increased phenytoin concentrations	In patients taking phenytoin and cenobamate, phenytoin demonstrated an increase in AUC of 84% and C_{max} of 70%. The AUC of cenobamate was decreased by 28%	A dose reduction of phenytoin will likely be required. The package insert recommends a slow dose reduction of up to 50%. Increased monitoring will be needed
Clobazam	Increased concentrations of the active metabolite of clobazam, desmethylclobazam	Desmethylclobazam is a substrate of CYP2C19, and increased concentrations should be expected	Decreased doses of clobazam may be needed

XCOPRI (cenobamate) [package insert]. Paramus, NJ: SK Life Science, Inc.; 2020.
Annals of Pharmacotherapy. 2021;55(3):318-29.

Cannabidiol (Epidiolex®)

- U.S. approval: 2018
- Plant-derived, purified pharmaceutical-grade cannabidiol (CBD)
- FDA approved indication: for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) in patients ≥1 year of age

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2021.

Mechanism of CBD for Seizures

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

The precise mechanisms by which EPIDIOLEX exerts its anticonvulsant effect in humans are unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.

- Proposed clinical mechanism
  - Modulation of intracellular calcium

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2021.

Controlled Substance Status

- Originally a Schedule I substance at the federal and state level
- Became a Schedule V substance in **2018** at the federal and state level
- Federally de-scheduled in **2020**; however, not adopted at state level in Pennsylvania

CBD Clinical Trial Data

Epilepsy syndrome	Dravet syndrome	Dravet syndrome	Lennox–Gastaut syndrome	Lennox-Gastaut syndrome	Tuberous sclerosis complex
Number of randomized patients	120	199	225	171	224
Treatment groups	20 mg/kg/d CBD Placebo	10 mg/kg/d CBD 20 mg/kg/d CBD Placebo	10 mg/kg/d CBD 20 mg/kg/d CBD Placebo	20 mg/kg/d CBD Placebo	25 mg/kg/d CBD 50 mg/kg/d CBD Placebo
Reduction in seizure frequency (primary endpoint)	Convulsive seizures CBD: 39% Placebo: 13% ($p = 0.012$)	Convulsive seizures 10 mg/kg/d CBD: 49% 20 mg/kg/d CBD: 46% Placebo: 27%	Drop seizures 10 mg/kg/d CBD: 37% 20 mg/kg/d CBD: 42% Placebo: 17%	Drop seizures 20 mg/kg/d CBD: 44% Placebo: 22% ($p = 0.01$)	All seizures 25 mg/kg/d CBD: 43% 50 mg/kg/d CBD: 37% Placebo: 20%
Responder rates (secondary endpoint)	Convulsive seizures CBD: 43% Placebo: 27% ($p = 0.08$)	Convulsive seizures 10 mg/kg/d CBD: 44% 20 mg/kg/d CBD: 49% Placebo: 26%	Drop seizures 10 mg/kg/d CBD: 36% 20 mg/kg/d CBD: 39% Placebo: 14%	Drop seizures 20 mg/kg/d CBD: 44% Placebo: 24% ($p = 0.004$)	All seizures 25 mg/kg/d CBD: 36% 50 mg/kg/d CBD: 40% Placebo: 22%

Clinical Drug Investigation. 2021;41:211-20. N Engl J Med. 2017;376: 2011-20.
JAMA Neurol. 2020;77:613-21. N Engl J Med. 2018;378:1888-97. Lancet. 2018;391:1085-96.

Dosing/Administration

- Dosage

Indication	Initial Dose	Dose Titration	Max Maintenance Dose
LGS or DS	2.5 mg/kg twice daily	Increase weekly by 2.5 mg/kg twice daily	10 mg/kg twice daily
TSC			12.5 mg/kg twice daily
Dose adjustment is recommended for moderate and severe hepatic dysfunction			

- Administration
  - oral solution at a concentration of 100mg/mL
- Beyond use dating
  - any unused portions should be discarded 12 weeks after opening the bottle

Epidiolex (cannabidiol) [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc.; 2021.

CBD Clinical Pearls

- Hepatically metabolized
  - substrate of CYP3A4 and CYP2C19
- Adverse Drug Reactions
  - somnolence, decreased appetite, diarrhea (20-30%)
  - thrombocytopenia*
  - elevated liver enzymes*

Table 2 Drug–drug interactions

Drug	Effect of CBD on plasma concentration	Effect on CBD plasma concentration
Brivaracetam	↑	n.a.
Clobazam	↑/↔	↔ (but 7-OH-CBD ↑)
n-Methylclobazam	↑↑	n.a.
Eslicarbazepine acetate	↑	n.a.
Levetiracteam	↔	n.a.
Rufinamide	↑	n.a.
Stiripentol	↔	↑
Topiramate	↑/↔	n.a.
* Valproate	↔	↔
Zonisamide	↑	n.a.

CBD cannabidiol, *n.a.* not available, ↑ elevation of plasma concentration, ↔ no change in plasma concentration

Clinical Drug Investigation. 2021;41:211-20.

Fenfluramine (Fintepla®)

- US approval: 2020
- C-IV
- FDA approved indication: for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients ≥2 year of age

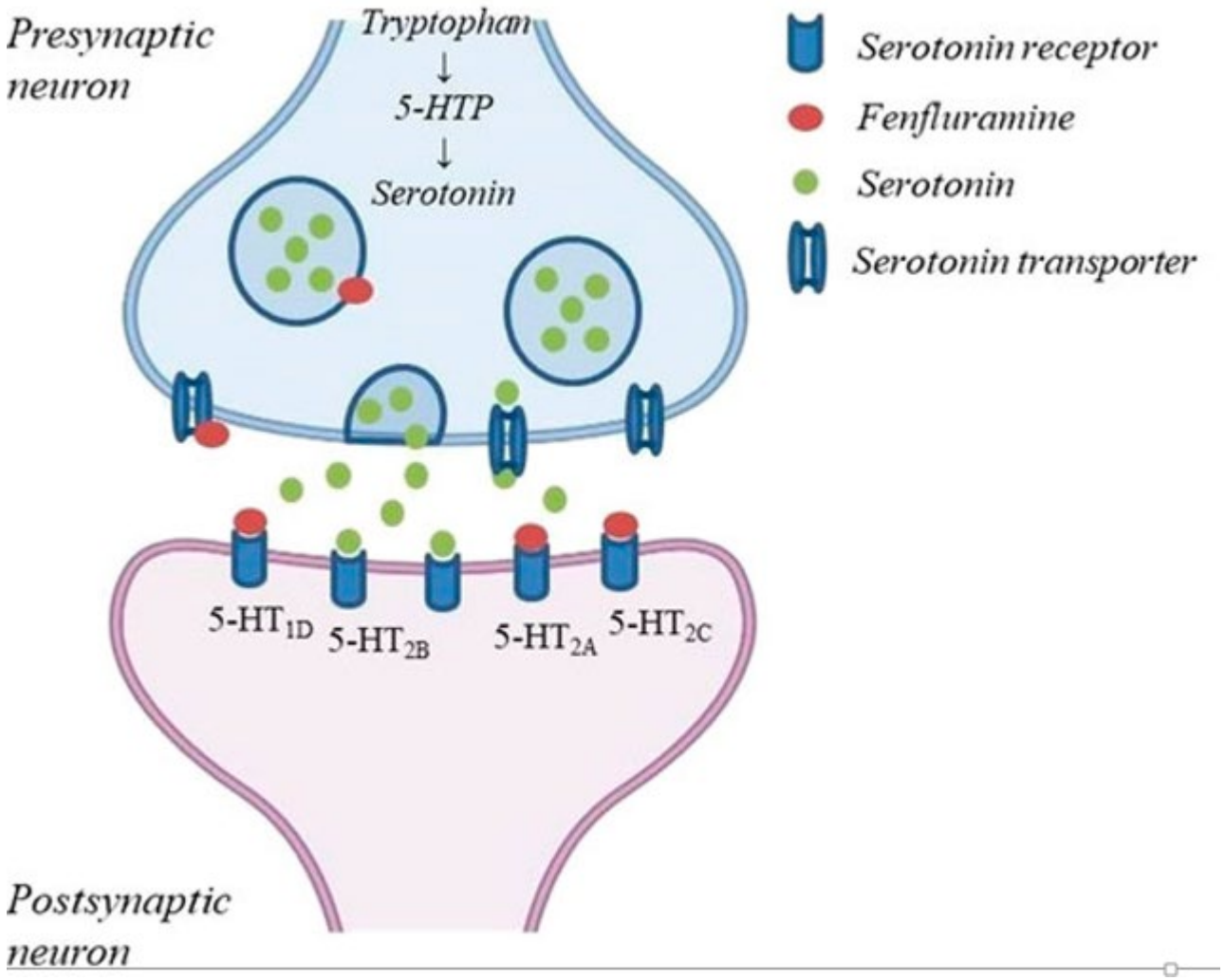
Fintepla (fenfluramine) [package insert]. Emeryville, Ca: Zogenix, Inc.; 2022.

History of Fenfluramine

- Originally used as a therapy for obesity
- Fen-Phen
- Removed from market 1997
  - valvular heart disease
  - pulmonary hypertension
- Research continued for seizures

Current Research in Pharmacology and Drug Discovery. 2022; doi: 10.1016/j.crphar.2021.10078

Fenfluramine Mechanism of Action



1. Targets serotonergic system
2. Regulates activity at sigma 1 receptors

Front Pharmacol. 2022; doi: 10.3389/fphar.2022.832929

Clinical Trial data

Dravet syndrome

FINTEPLA 0.7 mg/kg/day reduced monthly **convulsive seizures** by a median of 79.4% from baseline vs 16.5% for patients in the placebo group (*P*<.001; placebo-adjusted percent reduction was 70.0%)

Lennox-Gastaut syndrome (LGS)

FINTEPLA 0.7 mg/kg/day reduced monthly **drop seizure** frequency by a median of 23.7% from baseline vs 8.7% for patients in the placebo group (*P*=.0037)

Fintepla (fenfluramine) [package insert]. Emeryville, Ca: Zogenix, Inc.; 2022. finteplahcp.com

Adverse Drug Reactions

Side Effects	% Adverse Events [rank] in those Receiving Fenfluramine (Lagae et al., 2019) (N = 79)	% Adverse Events [rank] in those Receiving Placebo (Lagae et al., 2019) (N = 40)	% Adverse Events [rank] in those Receiving Fenfluramine (Nabbout et al., 2020) (N = 43)	% Adverse Events [rank] in those Receiving Placebo (Nabbout et al., 2020) (N = 44)	% Adverse Events [rank] in those Receiving Fenfluramine (Sullivan et al., 2020) (N = 232))	% Adverse Events [rank] in those Receiving Placebo (Sullivan et al., 2020) (N = 0)[†]
Patients with at least 1 adverse Event	94.9	65.0	97.7	95.4	89.7	N/A
Decreased Appetite	29.1*	5.0**	44.2*	11.4*	15.9*	N/A
Diarrhea	24.1*	7.5**	23.3*	6.8**	10.8*	N/A
Fall	5.1**	5.0**	0.0	0.0	0.0	N/A
Fatigue	10.1*	2.5**	25.6*	4.5**	0.0	N/A
Lethargy	13.9*	5.0**	14.0*	4.5**	0.0	N/A
Nasopharyngitis	13.9*	5.0**	16.3*	34.1*	19.4*	N/A
Pyrexia	11.4*	7.5**	25.6*	9.1**	21.6*	N/A
Seizure	8.9**	12.5*	4.7**	15.9*	11.2*	N/A
Somnolence	12.7*	7.5**	0.0	0.0	0.0	N/A
Upper Respiratory Tract Infection	10.1*	12.5*	0.0	0.0	10.3*	N/A
Vomiting	8.9**	10.0*	0.0	0.0	0.0	N/A
Weight Decrease	8.9**	0.0	0.0	0.0	0.0	N/A
Blood Glucose Decrease	0.0	0.0	14.0*	4.5**	0.0	N/A
Bronchitis	0.0	0.0	11.6*	4.5**	0.0	N/A
Abnormal Heart Valves	0.0	0.0	0.0	0.0	0.0	N/A

Current Research in Pharmacology and Drug Discovery. 2022; doi: 10.1016/j.crphar.2021.10078

Dosing Fenfluramine

Dravet Syndrome	
Initial Dose	0.1 mg/kg twice daily
Titration Dose (Day 7)	0.2 mg/kg twice daily
Maximum Dose (Day 14)	0.35 mg/kg twice daily

MAXIMUM TOTAL DAILY DOSE
26 mg

LGS	
Initial Dose	0.1 mg/kg twice daily
Titration Dose (Day 7)	0.2 mg/kg twice daily
Maintenance Dose (Day 14)	0.35 mg/kg twice daily

MAXIMUM TOTAL DAILY DOSE
26 mg

- Availability
  - oral solution at a concentration of 2.2mg/mL

Fintepla (fenfluramine) [package insert]. Emeryville, Ca: Zogenix, Inc.; 2022. finteplahcp.com

Fenfluramine Clinical Pearls

Drug Interactions	Safety
• Extensive hepatic metabolism • Active metabolite: norfenfluramine	• REMS • FinteplaREMS.com • Requires ECHO monitoring before treatment, every 6 months during treatment, and once 3-6 months after last dose

Fintepla (fenfluramine) [package insert]. Emeryville, Ca: Zogenix, Inc.; 2022.
Front Pharmacol. 2022; doi: 10.3389/fphar.2022.832929

Summary

- A variety of new AEDs have recently been approved
- Pharmacists will start seeing more prescriptions
- Having a basic understanding of their mechanism, efficacy, safety, scheduling, and availability is important

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Droperidol for Acute Agitation in the Emergency Department

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Objectives

- Review the epidemiology of acute agitation in the emergency department (ED)
- Discuss current pharmacotherapy options for the treatment of acute agitation in the ED
- Provide an overview on droperidol and its place in therapy
- Review safety and efficacy literature on droperidol use for the indication of acute agitation

Acute Agitation in the ED

- Acute agitation or hyperactive delirium is defined as altered mental status distinguished by disordered thinking and psychomotor agitation, often accompanied by a hyperadrenergic state
  - Altered mental status can include disorientation, defects in judgment or thought, and disruptions in perception, psychomotor skills, and behavior

- Validated tools:
  - Richmond Agitation Sedation Scale (RASS) of +4 (overly combative, violent, immediate danger to staff)
  - Altered Mental Status Score (AMSS) of 4 (combative, violent, out of control; loud outbursts of speech; agitated facial expression)

- Treatment goal: rapid achievement of adequate sedation is desired to minimize potential harm to both patients and staff

Hatten et al. ACEP Task Force Report; 2021.

Acute Agitation in the ED

- A 2018 study estimated a prevalence of 2.6% in 44,000 ED visits
  - 84% required physical restraint
  - 72% required sedation with intramuscular (IM) drug administration

- Prevalence of agitation visits can vary based on geographical location, services offered at hospital (psych or detox facility), or patient population

Miner et al. Ann Emerg Med. 2018

Acute Agitation in the ED

- Differential diagnosis:
  - Sympathomimetic toxidrome
  - Alcohol or sedative/hypnotic withdrawal syndrome/delirium tremens
  - Delirious mania
  - Serotonin syndrome
  - Neuroleptic malignant syndrome
  - Anticholinergic toxidrome

Hatten et al. ACEP Task Force Report; 2021.

Pharmacologic Options

- Ideal drug for acute agitation treatment:
  - Rapid onset
  - Moderate duration of action
  - Limited adverse effect profile- respiratory depression
- Currently, there is a lack of consensus for first line treatment
- Treatment options include:
  - Benzodiazepines
  - Antipsychotic- haloperidol, droperidol, olanzapine, ziprasidone
  - Ketamine

Hatten et al. ACEP Task Force Report; 2021.

Droperidol Overview

- First generation antipsychotic
- FDA approved for the treatment of post operative nausea and vomiting
- Used off label for acute agitation
  - Anti-dopaminergic neurotransmitter effects in midbrain, sub-cortical regions, and reticular activating system of the brain

Hatten et al. ACEP Task Force Report; 2021.

Droperidol Overview

- Adverse effects:
  - Extrapyramidal side effects- dystonia, akathisia
  - Neuroleptic malignant syndrome
  - Tardive dyskinesia
  - **Prolongation of QT interval**
    - FDA issued a Black Box Warning (BBW) in 2001 for potential QT prolongation leading to torsades de pointes
- Despite the BBW being based on post-marketing surveillance (49% of cases outside the US), droperidol use dropped drastically after the warning was issued
  - Sales fell by 90% within a year

Hatten et al. ACEP Task Force Report; 2021.
Richards et al. Cal J Emerg Med. 2003.

Droperidol Overview

- Since that time, multiple organizations have released statements on the use of droperidol reintroducing its use in emergency departments nationwide

Organization	Recommendation
American Academy of Emergency Medicine (AAEM), 2015	IM doses of droperidol up to 10 mg appear to be as safe and effective as other medications used for sedation of agitated patients; there is insufficient evidence to recommend mandating an ECG or telemetry for IV/IM doses <2.5 mg
American College of Emergency Physicians (ACEP), 2021	Droperidol starting at 5-10 mg IV/IM can be used for agitated psychosis, regardless of initial monitoring capability or ECG

Perkins et al J Emerg Med. 2015.
ACEP 2021

Pharmacokinetics

- **Administration**
  - IM or slow IV Push
- **Dose strengths and forms**
  - Solution, injection: 2.5mg/mL (2mL vial)
  - Solution, injection (preservative free): 2.5mg/mL (2mL vial)

	Droperidol (IV/IM)	Olanzapine (IM)	Haloperidol (IM)	Ketamine (IM)	Midazolam (IM)
Absorption	Rapid	Rapid	Rapid	Rapid	Rapid
Distribution	Vd (adults): 1.5L/kg	Vd: extensive 1000L	Vd: 9.5 to 21.7L/kg	Vd: 2.4L/kg	Vd: 1 to 3.1L/kg
Metabolism	Hepatic	Glucuronidation	Hepatic	Hepatic	Hepatic
Excretion	75% urine, 22% feces	57% urine, 30% feces	30% urine	91% urine, 3% feces	~90% Urine
Onset	3 to 10 minutes	15 to 45 minutes	15 minutes	10 to 15 minutes	~15 minutes
Duration	2 to 4 hours	2 hours	~2 hours	15 to 30 minutes	2 to 6 hours

Droperidol Safety

Author, Year	Design (n)	Dosing	Safety Outcome

Gaw, 2020	Retrospective cohort study (n=6353)	Median dose of 0.625mg
		• Droperidol administration for any indication
			• QTc prolongation
			  • 1.2% with QTc of ≥500 ms within 6 months prior to droperidol
			  • 0.7% with QTc of ≥500 ms within 24 hours after droperidol
			  • no fatal arrhythmias
			• No deaths attributable to droperidol

Cole, 2020	Retrospective chart review (n=16,546)	Dosing scheme not reported	**Critically Ill Patients** **Mean QTc Interval, (95% CI)** Before Droperidol 435.7 ms (426.7 to 444.7) After Droperidol 435.8 ms (427.5 to 444.1) **Non-Critically Ill Patients** **Mean QTc Interval, (95% CI)** Before Droperidol 424.3 ms (419.7 to 428.9) After Droperidol 427.6 ms (424.3 to 430.9)

Gaw et al. Am J Emerg Med. 2020
Cole et al. West J Emerg Med. 2020

Droperidol Efficacy

Author, Year	Design (n)	Dosing	Efficacy Outcome	Safety Outcomes
Isbister, 2010	Randomized control trial (n= 91)	• Droperidol 10mg (IM) • Midazolam 10mg (IM) • Droperidol 5mg/ Midazolam 5mg (IM)	Time security staff required (median, IQR) • Droperidol 10mg (20 mins, 11-37 mins) • Midazolam 10mg (24 mins, 13-35 mins) • Droperidol 5mg/ Midazolam 5mg (25 mins, 15-38 mins)	• No difference in incidence of respiratory events, hypotension, or abnormal QT-HR pairs. No dystonic reactions. • **Oversedation:** AMSS scores revealed both midazolam and droperidol/midazolam groups had unpredictable and deep sedation while droperidol alone resulted in consistent moderate sedation
Klein, 2019	Retrospective observational study (n= 15,918)	• Droperidol 5 mg (IM) • Olanzapine 10 mg (IM) • Haloperidol 5 mg (IM)	Rescue sedation administered within 1 hour of initial sedative • Droperidol- 11% • Olanzapine- 11% • Haloperidol- 18%	Droperidol group: • No cardiac events • 0.2% required intubation • 5 cases of akathisia and 2 cases of dystonia

Isbister et al. Ann Emerg Med. 2010
Klein et al. *J Emerg Med*. 2019

Droperidol Efficacy

Author, Year	Design (n)	Dosing	Efficacy Outcome	Safety Outcomes
Martel, 2021	Randomized double blind trial (n= 115)	• Droperidol 5 mg (IM) • Ziprasidone 10 mg (IM) • Ziprasidone 20 mg (IM) • Lorazepam 2 mg (IM)	Adequate sedation at 15 minutes: • Droperidol: 16/25 (64%) • Ziprasidone 10mg: 7/28 (25%) • Ziprasidone 20 mg: 11/31 (35%) • Lorazepam: 9/31 (25%)	Respiratory depression: • Droperidol: 3/25 (12%) • Ziprasidone 10 mg: 10/28 (36%) • Ziprasidone 20 mg: 12/31 (39%) • Lorazepam: 15/31 (48%) No patients had ventricular dysrhythmias QTc durations were similar in all group
Cole, 2021	Prospective observational study (n= 1257)	Droperidol 5mg (IM) Olanzapine 10 mg (IM)	Adequate sedation (AMSS ≤ 0) • No difference between groups before 15 minutes • AMSS scores higher for droperidol (median of -2) vs. olanzapine (median of -3) • Additional medications given for agitation- droperidol 17% vs olanzapine 24%	Droperidol group only (n= 538): • 23 cases of respiratory events (hypoxemia most common) • No incidences of torsades • Dystonia occurred in 4 patients and akathisia in 2 patients

Martel et al. Acad Emerg Med. 2021
Cole et al. Annals of Emergency Medicine. 2021

Conclusions

- Droperidol appears to be safe at doses ≤10 mg for acute agitation in the ER
  - Cardiac monitoring or EKG may not be necessary prior to giving medication
- Based on current available literature droperidol may have the following advantages over other medications used in the treatment of acute agitation:
  - Faster time to goal sedation
  - Decreased need for additional sedation medications
- More literature could be helpful in comparing droperidol to ketamine

References

1. Hatten B, Bonney C, Dunne R, et al. *ACEP Task Force Report on Hyperactive Delirium with Severe Agitation in Emergency Settings*.; 2021:132.
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BRIDGING THE FUTURE OF PHARMACY 2022

Septic Shock Updates: Fluids and Vitamin C

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Taking on Sepsis

- Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection
- Sepsis causes or contributes to 33-50% of in-hospital patient mortality and is responsible for as many as 11 million deaths worldwide annually
- Treatments options are routinely reviewed for impact on sepsis incidence and mortality
- 2021 Surviving Sepsis Campaign (SSC) Guideline update addresses for the first time:
  - Post-initial fluid resuscitation strategy
  - IV Vitamin C use

Crit Care Med. 2017;45(3):486-552.
Crit Care Med. 2021;49(11):e1063-e1143.

Initial and Continued Fluid Resuscitation Strategies

Surviving Sepsis Guideline: Fluid Updates

	2016 Update	2021 Update
Amount of initial fluid resuscitation	We **recommend** that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hour *Strong, low quality of evidence*	Changed recommendation from "we recommend" to **"we suggest"** verbiage *Weak, low quality of evidence*
Fluid Choice	We suggest using **either balanced crystalloids or saline** for fluid resuscitation of patients with sepsis or septic shock *Weak, low quality evidence*	For adults with sepsis or septic shock, we suggest using **balanced crystalloids instead of normal saline** for resuscitation. *Weak, low quality evidence*
Restrictive versus liberal fluid strategies		There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hour of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume **depletion after the initial resuscitation.**

Crit Care Med. 2017;45(3):486-552.
Crit Care Med. 2021;49(11):e1063-e1143.

Fluids: How much is too much?

- Early Goal Directed Therapy(EGDT) for the management of severe sepsis and septic shock ICU patients resulted in high volumes of fluids being administered

	Total Fluids (ml)	0-6 Hours	0-72 Hours
Rivers Trial	Standard therapy group	3499 ± 2438	13,358 ± 7,729
	EGDT group	4981 ± 2984	13,443 ± 6,390

- Concerns for patient harm with excess fluid administration including higher mortality shown in observational studies post-implementation of EGDT protocols
- 2016 SSC guidelines offered no guidance on the volume of IV fluid administration post initial resuscitation bolus
- Several trials from 2015-2019 investigated the risks and benefits of a restrictive vs. liberal resuscitation protocol for sepsis patients

N Engl J Med 2001; 345:1368-1377
J Crit Care. 2015; 30: 97-101.
Shock. 2015; 43: 68-73.
Crit Care Med. 2021;49(11):e1063-e1143.

Fluid Trials	Pilot Trial Design	Conclusion
Chen, et al. 2015	• Pilot study, n=82 • Septic shock ICU patients on vasopressors for 12 hours following initial fluids randomized to usual care vs. targeted fluid minimization (TFM)	TFM appeared to be safe, no difference in outcomes
CLASSIC Trial 2016	• Randomized, parallel-group, multicenter feasibility trial, n=151 • Septic shock ICU patients that received initial resuscitation randomized to fluid standard therapy vs. restriction group	Fluid restriction group successfully reduced volumes. Trend toward benefit with reduced fluid group but not powered to detect differences
REFRESH Trial 2018	• Randomized controlled pilot study, n=99 • Restricted fluid resuscitation regimen in first 6 hours after 1L fluids for patients with suspected sepsis and SBP <100mmHg	Restricted regimen was feasible Protocol deviations 12% vs 22% Illness severity of patients was low
RIFTS Trial 2019	• Pilot study, n=109 • Severe sepsis/septic shock ICU patients randomized to usual care vs. restrictive fluids (≤60 ml/kg of IV fluids) for first 72 hours	Restrictive strategy was able to be implemented using protocol driven treatment, no difference in outcomes

Chest. 2015; 148: 1462-1469.
Int Care Med. 2016; 42:1695-1705.
Int Care Med. 2018; 44:2070-2078.
Crit Care Med. 2019; 47:951-959.

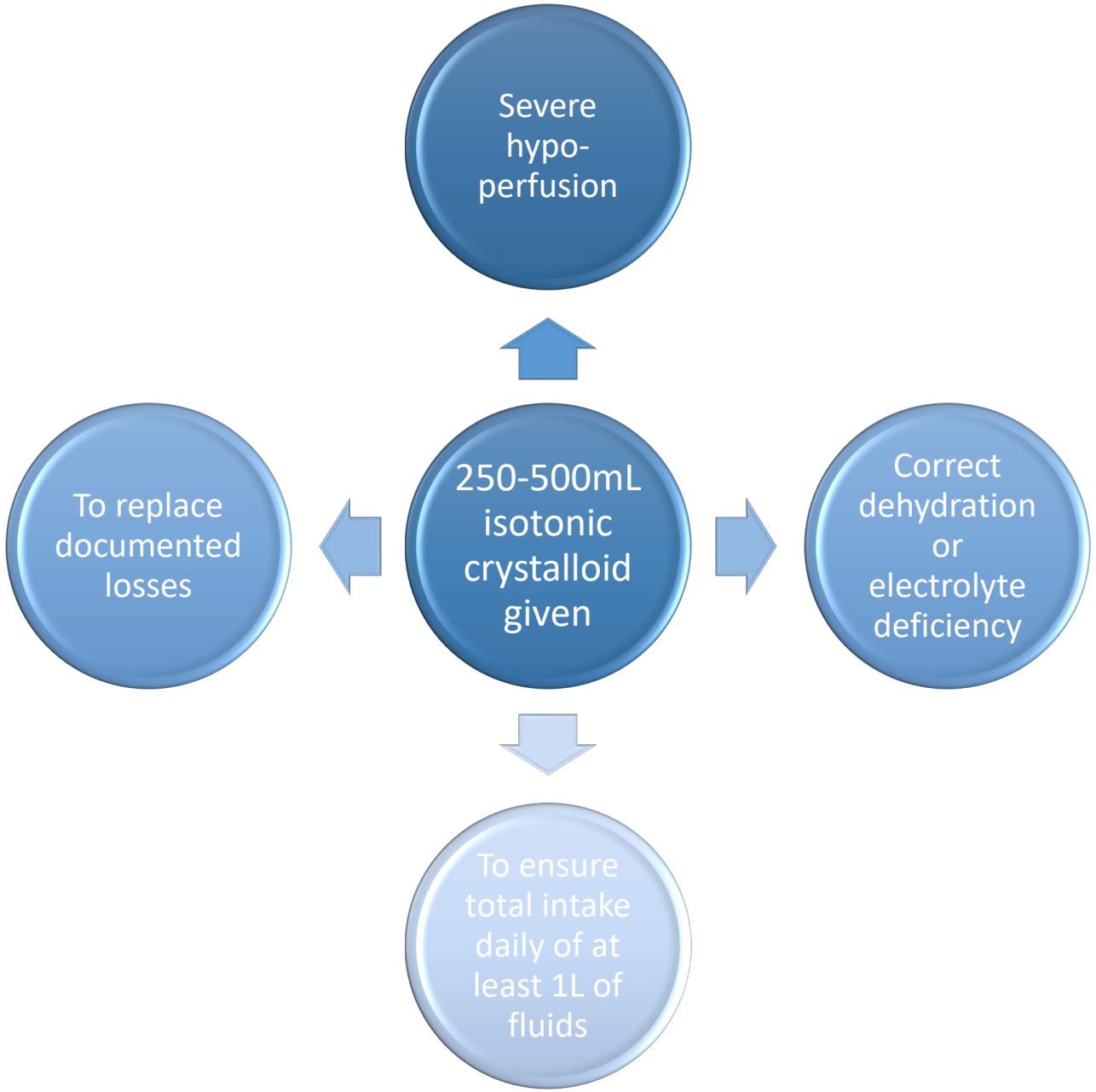
Pilot Trial Limitations

- Utilization of a restrictive IV fluid strategy varied with respect to:
  - Inclusion criteria
  - Definition of restrictive and liberal fluid strategies
  - Criteria guiding the administration of additional IV fluids (e.g., perfusion parameters vs. hemodynamic variables)
  - Duration of the interventions
  - Primary outcomes were mostly related to IV fluid volumes administered
- Given the small sample sizes, they were not powered to identify differences in patient-centered outcomes
- CLASSIC and CLOVERS trials are large randomized controlled trials investigating the same restrictive vs. liberal fluid approach

J Crit Care. 2015; 30: 97-101.
Shock. 2015; 43: 68-73.

CLASSIC Trial

- International, open-label, RCT of 1554 septic shock ICU patients randomized to either a restricted or standard fluid therapy
- Patients already received at least 1 liter of IV fluids and were randomly assigned if within 12 hours of shock onset
- Standard therapy group received fluids as long as documented improvement in hemodynamic factors
- Restrictive group protocol indicated criteria for when to bolus fluids when enteral route was contraindicated

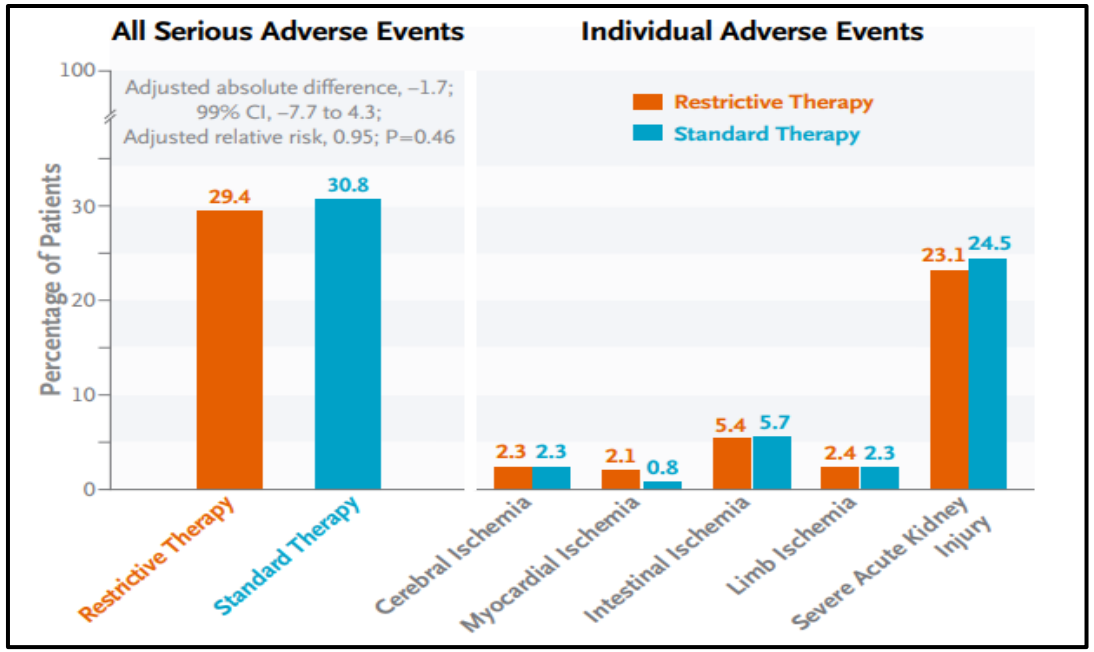


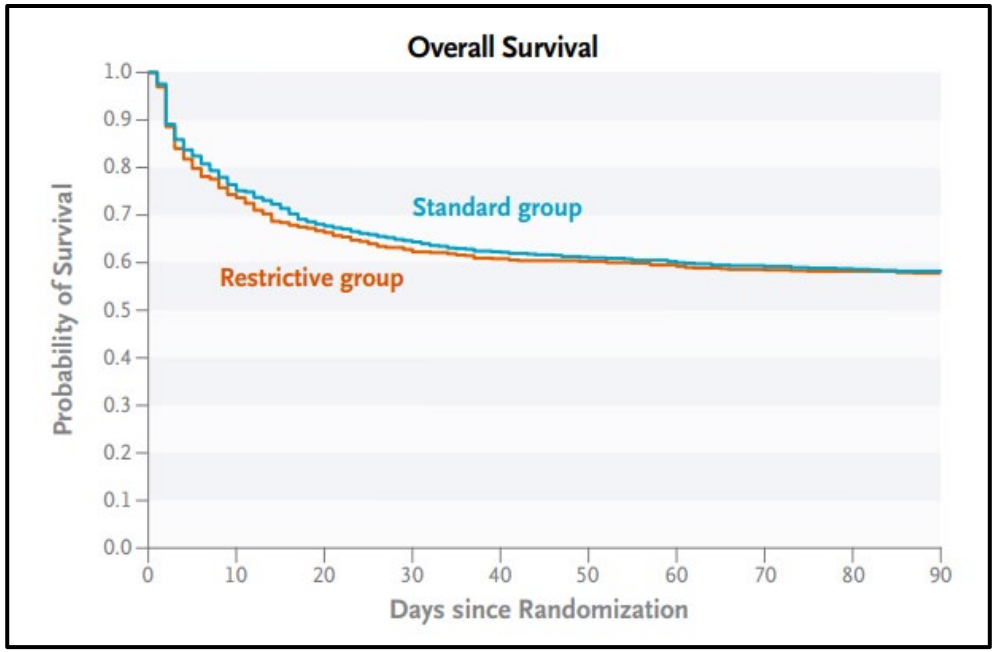
RCT= Randomized Control Trial

N Engl J Med. 2022; 386:2459-2470.

CLASSIC Trial Results

- At day 5, less than 1L difference in cumulative fluid amount received between groups
- Percentage of patients with at least one serious adverse event was similar
- No difference in median number of days alive without life support or number of days alive and out of the hospital
- Fluid restriction did not result in fewer deaths at 90 days compared to standard intravenous fluid therapy





N Engl J Med. 2022; 386:2459-2470.

CLASSIC Trial Considerations

- Patients and personnel were aware of group assignments
- Large volumes of fluid were administered outside of the trial protocol
  - ~3L in 24 hours prior to randomization
- No data regarding vasopressor dosing
- Large number of protocol deviations in both groups→ 21.5% in restrictive group vs 13.0% in standard group
  - Feasibility of protocol
  - Bolus volume of 250-500mL

Mean fluid volumes (ml)	Restrictive Group	Standard Group	Difference
Total fluid volume- Day 1	2,315	3,070	-755
Total fluid volume- Day 5	9,630	11,181	-1551
Cumulative fluid balance- Day 1	1,100	1,689	-589
Cumulative fluid balance- Day 5	2,297	3,187	-890

N Engl J Med. 2022; 386:2459-2470.

CLOVERS Trial

- Active Phase 3 trial estimated enrollment 2320 patients
- Hypothesis: Restrictive vs. liberal treatment strategy during first 24 hours of resuscitation for sepsis-induced hypotension will reduce 90-day in-hospital mortality

All patient receive 1-3L any isotonic crystalloid prior to enrollment

→

MAP goal not met?

Restricted group= vasopressors

Liberal group= 500mL boluses

→

Still not at goal?

Restricted group= rescue fluid boluses

Liberal group= Rescue vasopressors after 5L fluids given

- Interim analysis 2/2022: recruitment stopped, outcomes found to be similar in both arms and that further enrollment was unlikely to change the result
- Total of 1,566 recruited, trial results anticipated early 2023

CLOVERS: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis

Ann Emerg Med 2018; 72:457–466.
ClinicalTrials.gov NCT03434028

Intravenous Vitamin C Supplementation

Intravenous Vitamin C

- As a treatment option, IV Vitamin C offers:
  - Antioxidative effects that may mitigate tissue injury induced by oxidative stress in sepsis
  - Synergy with hydrocortisone in inflammatory cascade
  - Cause of renal oxylate crystallization at high doses → prevented with thiamine
- Marik et al proposed early use of a "Metabolic Resuscitation Protocol" was effective in preventing progressive organ failure, decreasing time on vasopressors, and lower mortality (8.5% vs. 40.4%) in severe sepsis patients
  - Retrospective before-after study of 94 patients

Chest 2017;151:1229-1238.
Crit Care Med. 2021;49(11):e1063-e1143.

IV Vitamin C: Initial Thoughts

- Low cost
- No identified major side effects
- Proposed mortality benefit
- Theoretical benefit for improvement in vascular tone and attenuation of organ dysfunction

- Requires IV line for administration
- Falsely elevated glucose monitor readings
- High doses can cause renal oxylate crystallization when used alone
- Findings have not been validated in an RCT

Chest 2017;151:1229-1238.
Crit Care Med. 2021;49(11):e1063-e1143.

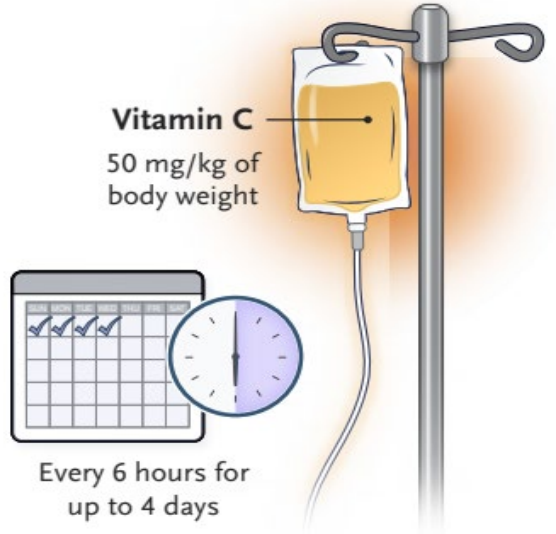
Intravenous Vitamin C Randomized Controlled Trials

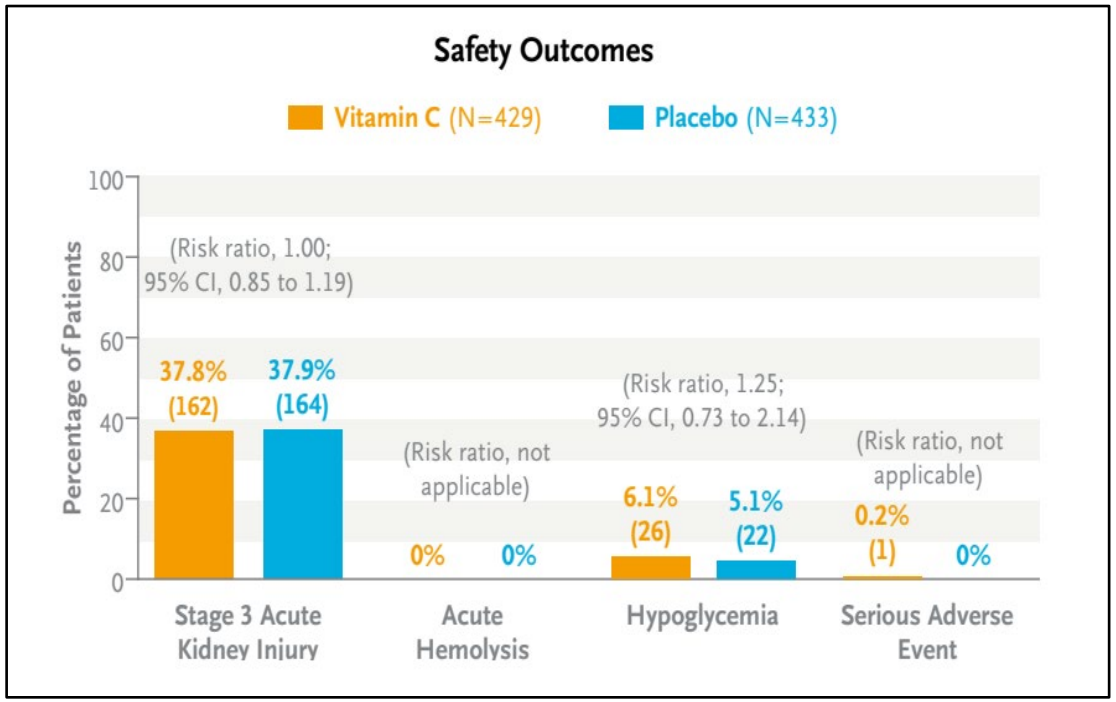
Trial	Patients Enrolled	Outcome	Results
CITRIS-ALI 2019	• 167	• SOFA 96 hours in acute lung injury	• No significant improvement in organ dysfunction scores or alter markers of inflammation and vascular injury • **28-day mortality: 46.3% placebo group vs 29.8% in the vitamin C group (P = .03)**
VITAMINS 2020	• 216	• Days alive and free of vasopressors	• No significant improvement in the duration of time alive and free of vasopressor administration over 7 days
HYVCTTSSS 2020	• 80	• 28 day mortality	• No difference in 28-day all-cause mortality was observed • The study was terminated after the midterm analysis
ORANGES 2020	• 137	• Time off of vasopressors	• **Statistically significant difference was found in time on vasopressors, indicating quicker reversal of shock (P < .001)** • Primary outcome was initially in-hospital mortality at study beginning
ACTS 2020	• 205	• SOFA 72 hours	• No statistically significant reduction in SOFA score during the first 72 hours, incidence of kidney failure, or 30-day mortality
ATESS 2020	• 111	• SOFA 72 hours	• No significant difference in change in SOFA scores between the treatment group and the placebo group
VICTAS 2021	• 501	• Consecutive ventilator- and vasopressor-free days	• No significant increase within 30 days • 30-day mortality was similar between groups • Early trial termination due to funding

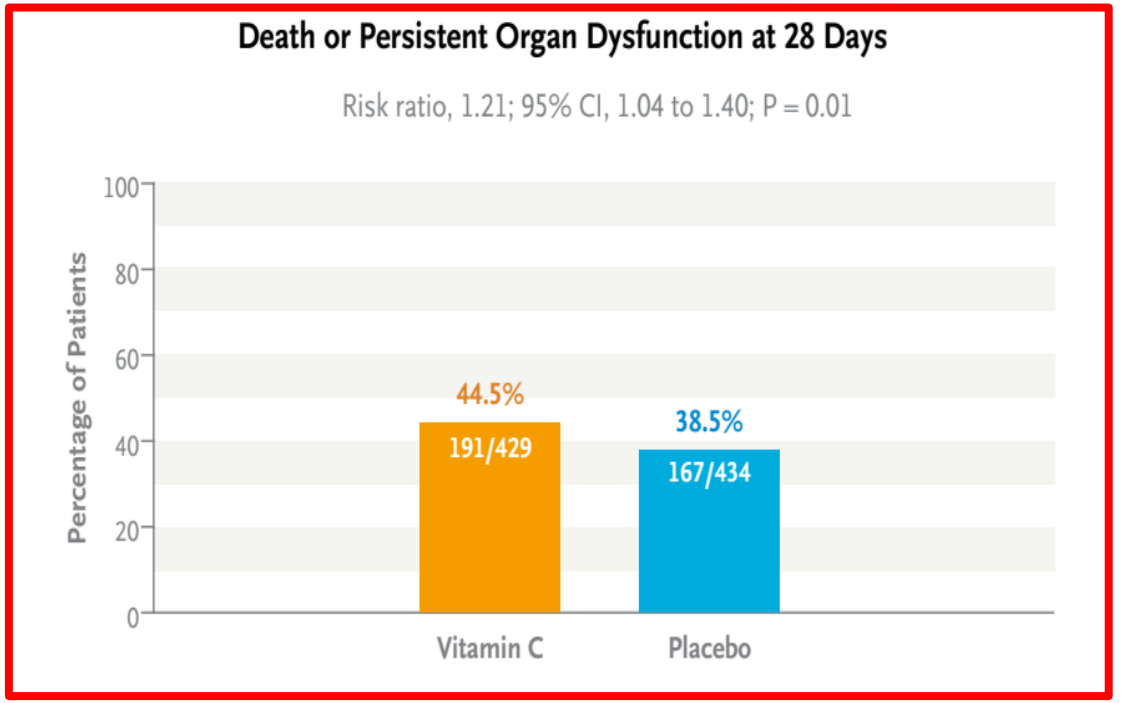
JAMA. 2019;322:1261-1270.
JAMA. 2020;323(5):423-431.
Chest. 2020; 158(1): 174-182.
Chest. 2020 Jul;158(1):164-173.
JAMA. 2020;324:642–50.
Int Care Med. 2020;46(11):2015-25.
JAMA. 2021;325:742-750.

LOVIT Trial

- International multicenter, parallel-group, blinded, RCT
- Included 863 patients in the ICU for <24 hours, concerned for infection as main diagnosis, actively receiving a vasopressor
- Intervention: Vitamin C (50 mg/kg IV) or matched placebo







N Engl J Med 2022; 386:2387-2398.

Trial	Inclusion	Results
Scholz, et al. 2021	• 17 studies • N= 3,133	• Pooled analysis indicated no mortality reduction in patients treated with IV vitamin C • Subgroup analysis → improved survival for treatment 3-4 days **(p=0.02)**
Sato, et al. 2021	• 11 studies • N= 1,737	• Not associated with a significantly lower short-term mortality • Associated with a significantly shorter duration of vasopressor use **(p < 0.01)** • Significantly greater decline in the SOFA score at 72–96 hours **(p < 0.01)**
Patel, et al. 2022	• 15 studies • N= 2,490	• Associated with a trend toward reduced overall mortality • High dose IV Vitamin C associated with a significant reduction in overall mortality (p = 0.03). Low-dose IV vitamin C had no effect • IV vitamin C monotherapy showed significant reduction in overall mortality **(p = 0.006)**, whereas there was no effect with combined therapy

Surviving Sepsis Guidelines	2016	2021
IV Vitamin C	No recommendation	For adults with sepsis or septic shock we suggest against using IV vitamin C. Weak, low quality of evidence

SOFA= Sequential Organ Failure Assessment

Crit Care. 2021;25:17. Crit Care. 2022; 26:3.
Crit Care Med 2022;50(3):e304-e312.

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2022 Updates in Clinical Pharmacy Practice

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