

The Prudent Prescriber

Phil Mohler, M.D. • pmohler69@gmail.com

2775 Crossroads Blvd • P.O. Box 10600 • Grand Junction, CO 81502-5600

May 2018

Nar-"CAN" we save more lives with naloxone?

Overdose deaths have doubled in Colorado over the last 20 years. Naloxone, an opioid receptor antagonist, has gained attention as a highly effective treatment for overdose. In fact, **naloxone improves the odds of surviving an overdose eightfold.** (Giglio 2015) In response, policymakers have improved insurance coverage and implemented standing orders that allow anyone to obtain naloxone from a pharmacy without a prescription. Despite these measures, Medicaid members only filled 36 prescriptions for naloxone in Mesa and the surrounding counties in 2017.

Why do prescribers not recommend this life-saving medication? The following are the most-cited barriers to prescribing, taken from two studies of Colorado health care professionals: time, stigma, moral hazard, formulations, and medicolegal issues. These barriers, besides time, are easily overcome.

To overcome stigma, many prescribers use drug-focused, rather than client-focused, language. For instance, "this medication comes with a risk of overdose, so I prescribe naloxone, the antidote for overdose, whenever I prescribe this pain reliever." Regarding moral hazard, numerous studies have shown that clients do not take greater risks. In fact, **clients report safer behaviors** after receiving a naloxone prescription. Regarding formulation, there is one preferred drug due to its extreme ease of use: nasal Narcan (details below). Medicolegally, there is no precedent for a physician being sued for prescribing naloxone; it is more likely that someone might be sued for not prescribing it. (Davis 2016)

Pharm Reps \neq Rational Prescribing

(PR)



(RP)

Antibiotics do NOT

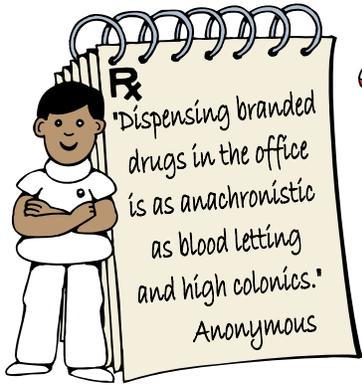


help acute bronchitis

β -blockers in post-MI save lives

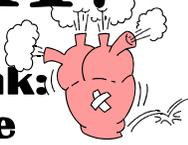


Pill splitters save BIG



CHE?

Think:
Ace
Aldactone
B-blocker
Dig
Diuretic



Avoid these expensive "me-too" drugs:

-  Intermezzo
-  Vimovo
-  Livalo
-  Gralise
-  Viibryd
-  Edarbi
-  Daliresp



Treat patients > 60 years to 150/90



NOW AVAILABLE
 ON THE
GENERIC MARQUEE

Viagra→sildenafil
 Effient→prasugel
 Strattera→atomoxetine
 Asacol HD→mesalamine DR
 Pristiq→desvenlafaxine

While there are perceived barriers, the lack of naloxone prescribing is certainly not due to lack of effectiveness. A recent study of EMS deployment of naloxone showed 93.5% of clients lived through the initial overdose, and **90% of those people were still alive a year later**. In a primary care setting, merely prescribing naloxone led to a remarkable 63% decrease in opioid-related ED visits in chronic pain clients. (Coffin 2016) Over 80% of clients filled the prescription, and 37% of them reported safer behaviors with opioids.

The cost-effectiveness of naloxone prescribing for chronic opioid users has not been completely established; however, naloxone distribution to people who use heroin is wildly cost-effective, with ICERs ranging from a few hundred to several thousand dollars. (Coffin 2013)

A recent publication by Colorado researchers suggested that the most important factors in predicting overdose in clients on chronic opioid therapy **are mental health diagnosis, substance use disorder diagnosis, and history of overdose**, with long-acting formulations and tobacco use as secondary risk factors. (Glanz 2018) The CDC adds to those risk factors higher opioid dosages (≥ 50 morphine equivalent doses daily) and concurrent benzodiazepine use. (CDC)

There are no contraindications to naloxone use. There is no risk of misuse; naloxone cannot get people "high". There is a risk of precipitated withdrawal, particularly for people with opioid use disorder. However, current doses usually do not precipitate severe withdrawal. Furthermore, clients need to be alive to go through withdrawal, so they've got that going for them.

While there are several formulations of naloxone, most pharmacies and insurance plans in Colorado have adopted Narcan nasal spray as their preferred formulation. This formulation costs about \$120 for a two-pack (co-pay: \$1 to \$10) and it is preferred for its extreme ease of use.

Bottom line:

- Consider "Narcan nasal spray 4 mg #1 administer prn suspected overdose" for:
 - Anyone with opioid use disorder OR
 - Anyone with history of overdose OR
 - Clients on chronic opioids with at least one of the risk factors mentioned above.
- For clients who do not want a prescription, let them know that they can always walk into a pharmacy and ask for naloxone without a prescription.
- For uninsured clients at risk for overdose, consider referring to Western Colorado Health Network in Grand Junction (970-243-2437), which distributes naloxone and training for free.
- Use naloxone to build trust with clients, opening a conversation about dose reduction and treatment if applicable.

J.K. Costello MD, MPH, works with the Steadman Group, a Denver-based, woman-owned consulting firm which is unaffiliated with the Vail orthopedic group. He is currently assisting Rocky Mountain Health Plans with developing their substance use disorder prevention and treatment initiatives in Western Colorado. He has no conflicts of interest in discussing Narcan or any other drugs.

Cognitive Enhancers for Treating Alzheimer's disease: A New Look, Same Dismal Results

Physicians always want to "fix" things. While sitting across from patients with progressive cognitive decline, it was always difficult for me not to pull out the prescription pad. My heart said, "Yes." The accumulated evidence for the efficacy of cognitive enhancers (donepezil {Aricept} and its cholinesterase inhibitor cousins and memantine {Namenda}) said, "No."

Andrea Tricco *et al*/and her Canadian colleagues present a Systematic Review and Network Meta-analysis of 142 studies that includes 110 randomized controlled trials (RCTs), 21 non-RCTs and 11 cohort studies [The Journal of American Geriatrics, January 2018]. None of the authors reported a conflict of interest.

This is an exhaustive study utilizing Network Meta-Analysis (NMA), a technique that is being found in increasing numbers in the literature because of its ability to examine all potential treatments. NMAs provide summary treatment effects for pairwise treatment comparisons even if these treatments have never been compared directly in a study. NMAs provide the opportunity to rank each included treatment for the outcome examined. The validity of NMA analyzes rests on the assumptions that the included trials have similar characteristics across treatment comparisons.

Results:

1. Risk of bias: 60% of the RCTs had unclear adequate allocation concealment; 70% had selective outcome reporting; 53% had a high risk of incomplete outcome bias because of the large number of dropouts; and 56% had a high potential risk of other bias, like funding.
2. The cognitive enhancers have minimal effects on cognition. Only donepezil met the effect size criteria for the ADAS-Cog cognition outcome and it was a small effect. Only galantamine (Razadyne) improved overall global status and only minimally.
3. None of the cognitive enhancers alone or in combination were likely to improve participants' functional status.
4. The cholinesterase inhibitors increased the risk of gastrointestinal harms and headaches. These harms are significant and caused substantial numbers of participants to drop out of the studies.

My Take:

- Given the multiplicity of drugs, measuring tools and clinical endpoints, it is statistically likely that this analysis would show a positive result in at least one study, even when there is none.
- Adding in the biases noted above, plus the heterogeneity of the patients in the studies, it is highly likely that even the small cognitive and global benefits were overestimated.
- Do not prescribe these very low value drugs!

Bonjesta PUQing in Pregnancy Has Greed No Bounds?

The combination of doxylamine succinate, a first generation antihistamine and pyridoxine hydrochloride, a vitamin B6 analog has been around since 1956 as Bendictine. In 1983 Merrell Dow Pharmaceuticals voluntarily removed Bendictine from the market due to high litigation costs. Subsequently, the FDA ruled the drug was **not** teratogenic.

Banking:

Now Duchesnay USA, banking on the American College of Obstetricians and Gynecologists (ACOG) pronouncement that this vitamin/antihistamine combo (Pregnancy Category A) is first line therapy for the nausea and vomiting of pregnancy has released a second pyridoxine/doxylamine combination—Bonjesta.

Bonjesta has 20mg of each of the two components, doubling the doses of both drugs of their initial offering, Diclegis.

Study:

There were no new studies of Bonjesta.

A single randomized, double blind, placebo-controlled multicenter study of 261 nauseous, vomiting women at 7 to 14 weeks of pregnancy brought Diclegis to market. Utilizing the pregnancy unique quantification of emesis (PUQE) score, Diclegis reduced symptoms 0.7 better than placebo on a 3-15 point scale. For those of you intent on developing expertise in this arena, the PUQE score incorporates the number of daily vomiting episodes plus the number of daily heaves plus the length of daily nausea in hours for an overall score rated from 3 (no symptoms) to 15 (most severe). Over the treatment period, 19% of Diclegis treated patients remained on 2 tabs per day, 21% received 3 tabs per day and 60% received 4 tabs daily.

Cost:

Duchesnay is selling Bonjesta for \$12.34 per tablet with a maximum dose of 2 tablets per day (equivalent to the most common dose of Diclegis). That's \$25 a day or \$750 a month.

Another approach is to recommend OTC doxylamine (\$0.16/25mg tab) and OTC pyridoxine (\$0.05/25mg tab) for a comparable maximum dose of \$0.42 per day or \$12.60 per month.

My Take:

- The single crappy little study (CLS) that brought Diclegis to market suggests minimal efficacy.
- I do love the sense of humor of the scientists? marketers? promoting their "PUQE" score.
- My French is nonexistent, but Bonjesta suggests "Good Joke." Let's hope that the "Joke" is on avaricious Duchesnay USA and that no pregnant patient or her health insurer ever buys these two products.

You may access previous issues at <https://www.rmhp.org/i-am-a-provider/provider-resources/publications-for-providers>.

DISCLAIMER: The information and statements contained in "The Prudent Prescriber" constitute the opinions of its author, unless otherwise noted. Nothing contained in "The Prudent Prescriber" is intended to demonstrate, indicate or suggest that any person or company is incompetent or unfit. Likewise, nothing contained in "The Prudent Prescriber" is intended to damage the business, business relationships, business dealings or reputation of any person or company.