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Acetaminophen: Not the Safest Drug in the World?

I've long proclaimed acetaminophen, "Safest Drug in the World" and recommended it over NSAIDs as the go-to medication for over-the-counter management of pain and fever. Orandi's et al. study in JAMA March 7, 2023, provided a new perspective for me. Although acetaminophen has a remarkable safety record when taken as directed, its use has been associated with a huge public health burden.

- 112,000 Poison Control Center calls and 60,000 hospitalizations in the US annually.
- It is the leading cause of acute liver failure in the US and many other high-income countries.
- 40% to 58% of acute liver failure cases due to acetaminophen hepatotoxicity are unintentional, with many involving combination acetaminophen and opioid/cold products.

Cashin et al. in a synthesis of the Cochrane Reviews of Pharmacological Treatments for Low Back Pain (Cochrane Database Syst Rev 2023 April 4) concluded with high certainty evidence for no evidence of difference between acetaminophen and placebo. For safety, the authors found very low - and high- certainty evidence for no evidence of difference between NSAIDs and acetaminophen compared to placebo for risk of adverse events.

Public health efforts in both the UK and the United States directed toward limiting available doses of acetaminophen have had some effect on decreasing morbidity and mortality. In September 1998, legislation in the UK limited the sale of acetaminophen to 32 tablets per sale in pharmacies. Other retail outlets could sell a maximum of 16 tablets. (In Ireland, it's 24 tablets and 12 tablets, respectively.) In comparing the 12 months before the limitation of numbers of tablets and the 12 months after the law's implementation, the number of acetaminophen deaths in the UK fell from 185 to 147 (21%). After the legislation 66% fewer patients underwent liver transplantation because of acetaminophen poisoning of the liver.

In January 2011 the US FDA announced a mandate to limit acetaminophen to 325 mg per tablet in combination with opioid medications, as well as a boxed warning. The percentage of acute liver failure cases involving acetaminophen and opioid toxicity increased 7% per year prior to the announcement and decreased 16% per year after the announcement. The analysis was unable to identify if the decline in toxicity was due to the boxed warning, limiting the dose, or both.



Two observations:

I recently presented a class to seniors sharing the OTC products in my medicine cabinet. Acetaminophen was on the list. The bottle sitting in my medicine cabinet contained 600 of the 500 mg size of acetaminophen. (Sam's Club brand \$11.34) That is 300,000 mg of acetaminophen or more than two LD₅₀ doses for a 70 kg person. Buying a couple of lethal doses of acetaminophen is almost as easy as buying a gun in Mesa County, Colorado.

Should we in the US take a page out of the Brit's playbook and significantly limit the number of acetaminophen tablets per sale?

A trip to a local pharmacy recently revealed that a 12-ounce bottle of NyQuil (\$9.79) contains, in addition to dextromethorphan and doxylamine, 650 mg of acetaminophen per 30cc. The dose on the bottle suggests 30cc every 6 hours for adults and children over 12 years of age. It's easy to see how an adult with rip-roaring respiratory symptoms of Covid/flu/common cold could easily consume 2600 mg of acetaminophen in 24 hours from the NyQuil and an additional 4000 mg a day from acetaminophen tablets.

The issue of what is a safe dose of acetaminophen remains unanswered. Product labels advise 4 g/24 hours and 3g/24 hours for those over 65 years. The safety of the drug is influenced by many factors including age, genetics, nutritional status and alcohol intake. A study by Watkins et al. (JAMA 2006; 296 (1) 87-93) showed that at the recommended dose of 4 g per day alanine aminotransferase level elevations were more than three times the upper limit of normal in 31% to 44% of persons receiving acetaminophen!

If you were running the FDA, would you take acetaminophen out of all cold products as well as opioid combinations?

For now, we're stuck with reminding patients on opioid/acetaminophen combos and for patients buying over-the-counter cold and flu medicines to limit acetaminophen doses.

Short & Sweet

- **Blood pressure medicines at bedtime**

I got it wrong again. Several months ago, I quoted a study that showed that evening dosing with anti-hypertensive therapy had better outcomes than morning dosing. I thought it was a game changer. I started taking my lisinopril at bedtime. Now a prospective, parallel group study (TIME study) reported in the Lancet (October 22, 2022) that when 21,104 adults with hypertension, followed for a mean of 5.2 years, were randomly assigned to evening or morning dosing groups, there was no difference in terms of major cardiovascular outcomes.

- **Best treatment for diabetic peripheral neuropathic pain (DPNP)**
The OPTION-DM trial (Lancet August 27,2022) randomly assigned 140 patients with DPNP to head-to-head comparisons of amitriptyline, pregabalin, and duloxetine. The three drugs had equal efficacy in treating patients with painful diabetic neuropathy over at least 50 weeks. All two drug regimens boosted response rates modestly. Half the patients did not have a meaningful clinical response. All three drugs are available as generics for less than \$15 per month at the highest doses used in the study.
- **And some good news**
Latuda (lurasidone), the most utilized branded anti-psychotic, went generic in February 2023. The patent expired and the price dropped from \$47.29 per tablet to \$0.67-\$2.04 per tablet.
- **Effects of Covid-19 vaccination during pregnancy**
In a systematic review and meta-analysis (Rev Med Virol. 2023 March 10) the authors evaluated 30 studies involving 862,272 pregnant individuals (308,428 vaccinated and 553,844 unvaccinated).
Results:
 - Reduced risk by 60% of COVID-19 infection in pregnant women associated with vaccination.
 - Reduced risk of COVID-19 hospitalization during pregnancy by 53% and COVID-19 ICU admission by 82% associated with vaccination.
 - The risk of stillbirth was reduced by 45% in association with vaccination.
 - There was no evidence of a higher risk of adverse outcomes with vaccination including miscarriage, gestational diabetes, gestational hypertension, cardiac problems, polyhydramnios, unassisted vaginal delivery, C-section, postpartum hemorrhage, gestational age of delivery, placental abruption, Apgar score at five minutes, below 7, neonatal fetal abnormalities, or low birthweight.
- **Inhaled steroids plus albuterol as rescue therapy for patients with moderate-to-severe asthma**
US and international guidelines recommend inhaled corticosteroids/formoterol (generic Symbicort \$97-\$210/month) as maintenance and rescue therapy in patients with moderate to severe asthma. Two studies both published in NEJM (June 2, 2022; 386:2071 and April 21, 2022; 386:1505) demonstrated that using as needed inhaled corticosteroids in teenagers and adults with moderate to severe asthma was effective. The studies used albuterol/ budesonide or albuterol/beclomethasone. Both trials demonstrated significantly fewer severe asthma exacerbations compared to the albuterol alone group or placebo group. Clinical trials are underway for combined ICS/albuterol products.

TB or not TB

TB or not TB, that is the question:

Whether it's overt in the kind of suffering
That slings the acid-fast infectious darts' misfortune
Or makes its harms a sea of troubles
That not opposed them die nor sleep.
No more! The sleeping node we aim to end,
Or hearty as the thousand natural stocks
That flesh is heir to dread consumption,
Devouring the wealth to death, to sleep.
To sleep eternal, no chance to dream of more heart's throb
For in that sweat of sleep what wasting dreams may come,
Where we have shuffled off the mortal cough
Thus paused through pharmaceutic interjects
To stave calamity off for longer life.

For case and contacts, over space and time
Suppress the wrong on man's long untimely
Pangs of despised blood in lungs' decay.
Insouciance of ignorance and spurns
The patient's merit as unworthy takes
Then the selfsame in quietness of fear
That bears toward "others" whose bundles bear
And grunt and sweat their weary life
In dread of death something hereafter
Their undiscovered country where born
The travelers' turns puzzle them still
And takes us farther to cure ills they have
Than fly them over to where we know not
Our conscience dost cower 'mongst us all.
Non-native hues of consternation
Of sickly poor with ails past bought
Their IGRA test or TST of this moment
In our realm of current philanthropy
In the name of self-preservation take action.

By: Thomas Orr

Tom is a regional epidemiologist with the Mesa County Colorado Health Department. His poetry often reflects his workaday world. He reminds us that active tuberculosis is still with us. "TB or Not TB" is printed with permission of the author.

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