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THE BRASS TACKS: CONCISE REVIEWS OF PUBLISHED EVIDENCE

Neuraminidase inhibitors for treatment of influenza

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Keywords: influenza, neuraminidase inhibitors, oseltamivir, zanamivir

NNT color recommendation	Yellow (unclear if it provides benefit)
Summary heading	May reduce the duration of symptoms by less than 1 day but are associated with adverse events
Benefits of NNT	Shorter duration of symptoms by less than 1 day (14–17 hours) in adults treated with neuraminidase inhibitors compared to placebo No reduction in hospitalization or disease complication (e.g., pneumonia)
Benefits in percentages	No reduction in hospitalization or disease complication
Harms of NNT (NNH)	1 in 28 adults was harmed (nausea) 1 in 22 adults was harmed (vomiting) 1 in 19 children was harmed (vomiting)
Harms in percentages	3.6% higher risk of nausea in adults 4.5% higher risk of vomiting in adults 5.3% higher risk of vomiting in children
Efficacy endpoints	Hospitalization and time to symptom alleviation
Harm endpoints	Adverse events (e.g., nausea, vomiting, and neuropsychiatric events)
Who was in the studies	Treatment: adults and children with confirmed or suspected to have influenza and also those with confirmed or possible exposure to influenza.

NARRATIVE

Neuraminidase inhibitors (NAIs) are commonly used in the prevention and treatment of influenza. Previous studies and reviews have demonstrated a questionable and modest benefit of their use while demonstrating potential adverse effects.[1,2]

The most recent Cochrane review discussed here[3] analyzes the data from randomized controlled trials evaluating the effects of NAIs in children and adults with confirmed or suspected exposure to influenza. The systematic review included trials testing the effectiveness and safety of two commonly used NAIs, oseltamivir (Tamiflu) and zanamivir (Relenza). Twenty-three oseltamivir trials were included, with a total of 9,623 subjects (6,574 in treatment trials and 3,049 in prophylaxis trials) with ages ranging from 1 to 82 years. Twenty-eight zanamivir trials were included, with a total of 14,628 subjects (7,678 in treatment trials and 6,950 in prophylaxis trials) with ages ranging from 5 to "over 65." The authors' novel methodology for study selection was complicated. All of the included trials were industry-supported randomized control trials (RCTs) comparing oseltamivir or zanamivir versus placebo, some of which were unpublished reports from manufacturers (hence not peer-reviewed). Studies were excluded if they were not placebo RCTs, were pharmacokinetic studies, were dose comparison studies, or were ongoing trials.

The authors of the Cochrane systematic review state that they are not convinced they had access to all existing manufacturer data. They report higher risk of bias with frequent lack of reporting of random sequence generation methods, incomplete data (symptoms, complications, and safety data), and concern for lack of full blinding of participants and personnel.[3] The Cochrane review included trials that enrolled previously healthy children or adults diagnosed with influenza (with or without symptoms) for the treatment analysis and

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similar populations who took NAIs for prophylaxis (with or without exposure).

The primary outcome measures for treatment analysis were: 1) symptom relief, 2) hospitalization, and 3) harms. The primary outcome measures for prophylaxis analysis were 1) influenza (symptomatic and asymptomatic, with laboratory confirmation) and influenza-like illness (ILI) and 2) hospitalization.

Treatment

In adults, oseltamivir reduced time to first alleviation of symptoms by 16.8 hours (95% CI = 8.4 to 25.1 hours). Zanamivir reduced the time to first alleviation of symptoms in adults by 14.4 hours (95% CI = 9.4 to 19.2 hours). In healthy children, based on a single study, oseltamivir reduced the time to first alleviation of symptoms by 29 hours. However, in asthmatic children, there was an increase in time to first alleviation of symptoms by 5.2 hours (95% CI = 11.1 hours lower to 21.4 hours higher). Standard asthma medical care and close follow-up may overshadow the incremental benefit of oseltamivir in this specific population. The effect of zanamivir on time to first alleviation of symptoms in children was not statistically significant. Data for asthmatic adults were not reported. Oseltamivir treatment did not reduce the risk of hospitalization in children or adults.

Serious adverse events or those leading to withdrawal from the study were higher in treatment groups. Oseltamivir treatment in adults was associated with nausea (relative risk [RR] = 1.57, 95% CI = 1.14 to 2.15, absolute risk difference [ARD] = 3.7%, number needed to harm [NNH] = 28) and vomiting (RR = 2.43, 95% CI = 1.75 to 3.38%, ARD = 4.56%, NNH = 22). Vomiting was also seen in pediatric studies (RR = 1.70, 95% CI = 1.23 to 2.35, ARD = 5.3%, NNH = 19). There was no significant increase in the risk of neuropsychiatric events during treatment.

Oseltamivir reduced self-reported, unverified pneumonia (RR = 0.55, 95% CI = 0.33 to 0.90). The lack of clear pneumonia definitions across studies make this outcome unreliable. There was no reduction in pneumonia with zanamivir. Neither oseltamivir nor zanamivir reduced incidence of sinusitis, bronchitis, or otitis media.

Prophylaxis

Oseltamivir prophylaxis was initiated on the basis of "local outbreaks," which were not well elucidated. Patients generally took the medication for 6 weeks. Zanamivir prophylaxis was initiated based on population characteristics (e.g., patients in nursing homes) without an indication based on direct exposure or local outbreaks. Patients were treated for 28 days. There were no pediatric prophylaxis studies.

The studies reporting the benefits of NAIs for prophylaxis were of low quality (significant biases), had small sample sizes, and did not clearly define the indications for giving prophylaxis. Therefore, we are refraining from reporting the data for this particular indication here.

CAVEATS

The use of NAIs for the treatment of influenza in adults confers a small decrease in time to symptom alleviation (17 hours). The statistical heterogeneity for the treatment analysis was reported to be low. The Cochrane review employed the use of clinical study reports from national drug regulators, in addition to studies published in biomedical journals. This resulted in a comprehensive study that better represents the effects of these medications. Although the meta-analysis only included RCTs, limitations such as selective publication, inclusion of non–peer-reviewed data, and high attrition rates negatively impacted the quality of the evidence. A subgroup analysis on the treatment effect of zanamivir between influenza-positive and influenza-negative patients revealed that both populations had an identical duration of reduction in symptoms. A recent open-label RCT published in January 2020 (the ALIC4E trial[4]) also showed that patients with symptomatic influenza treated with oseltamivir plus usual care recovered 1 day (95% CI = 0.74 to 1.31 days) sooner than those who received usual care alone. As demonstrated in the Cochrane review, this reduction occurred equally in influenza-positive and influenza-negative groups, irrespective of laboratory-confirmed influenza. This suggests that NAIs most likely do not have an influenza-specific effect in symptom alleviation or as likely that this was a placebo effect given that the study was unblinded and patients knew if they were receiving an NAI. The use of NAIs in healthy children may reduce time to symptom alleviation by about 1 day, but carries the risk of adverse events.

The systematic review did not report outcomes where incidence was less than 0.5%, and this included mortality. Lack of clarity regarding mortality is unfortunate, given the estimated 200,000 to 600,000 annual deaths worldwide due to influenza.[5] It is important to note that the Infectious Diseases Society of America (IDSA)[6] and the Centers for Disease Control and Prevention (CDC)[7] endorse the consideration of NAIs for all people with ILI within 48 hours of onset. These groups recommend NAIs for all persons at higher risk of dying from influenza (i.e., immunocompromised status, advanced age, multiple comorbidities) and for all persons hospitalized with influenza. These recommendations are based on observational data and expert opinion. Unfortunately, we do not have strong data to support these recommendations, and given their widespread use, it is difficult to imagine that we will see a RCT in the future, answering the questions "Do NAIs save lives?" or "Is there a benefit with NAIs in people who are very sick (hospitalized)?"

The data for NAIs are further confounded by the financial conflicts of interest that are present in many of the studies on NAI use. Dunn et al.[8] demonstrated that among NAI studies associated with a FCOI, 88% of the studies were classified as favorable. For those without FCOI (among which was this Cochrane review), 17% of the

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studies were classified as favorable. Thus, much of the positive data regarding NAI are heavily biased.

In summary, the existing data indicate that NAIs reduce the duration of symptoms by less than 1 day in patients with confirmed or suspected influenza. The use of NAIs to treat influenza does not prevent hospitalization and is associated with adverse events. Therefore, we have assigned a color recommendation of yellow (unclear if it provides benefit, more data needed) to this treatment.

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REFERENCES

1. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*. 2009;8(339):b5106.
2. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev*. 2006;(3):CD001265.
3. Jefferson T, Jones MA, Doshi P, Del Mar CB, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database Syst Rev*. 2014;2014(4):CD008965.
4. Bongard E, van der Velden AW, Cook J, et al. Antivirals for influenza-like illness? A randomised controlled trial of clinical and cost effectiveness in primary CarE (ALIC4E): the ALIC4 E protocol. *BMJ Open*. 2018;8(7):e021032.
5. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*. 2018;391(10127):1285.
6. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1.
7. Centers for Disease Control and Prevention. Influenza antiviral Medications: Summary for Clinicians. 2020. Accessed December 30, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
8. Dunn AG, Arachi D, Hudgins J, Tsafnat G, Coiera E, Bourgeois FT. Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza: an analysis of systematic reviews. *Ann Intern Med*. 2014;161(7):513-518.

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