NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Journal of Education, Health and Sport. eISSN 2391-8306.

Journal Home Page
https://apcz.umk.pl/JEHS/index

BENDER, Aleksandra, WIDOMSKA, Katarzyna, BERNAD, Mateusz, WALCZAK, Paulina, SZYMULEWICZ, Bartłomiej, ŁUKASZEWICZ, Jakub, GAŁACH, Magdalena, DĄBROWSKI, Kacper, NIEWĘGŁOWSKA, Małgorzata, and KRAZIŃSKA, Oliwia. Oseltamivir Monotherapy Compared with Combination Therapy Including Oseltamivir for Influenza – A Systematic Review. Journal of Education, Health and Sport. 2026;89:69767. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.89.69767

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 12.03.2026. Revised: 17.03.2026. Accepted: 19.03.2026. Published: 26.03.2026.

Oseltamivir Monotherapy Compared with Combination Therapy Including Oseltamivir for Influenza – A Systematic Review

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ABSTRACT

Background. Influenza is considered by scientists and practicing physicians as a significant health problem, often leading to a variety of complications. One of the most commonly used treatments for influenza is oseltamivir. However, due to constantly changing influenza virus serotypes, oseltamivir treatment is sometimes insufficient. Therefore, researchers are investigating for new, more effective therapeutic approaches.

Aim. The aim of this study was to determine whether a combination therapy including oseltamivir is more effective than monotherapy.

Material and methods. We screened original articles evaluating virological and clinical outcomes of oseltamivir combination therapy, as well as publications investigating treatment with higher doses of oseltamivir. Data were collected from PubMed, Web of Science and Google Scholar. We defined the study population as adults with symptomatic and laboratory-confirmed influenza.

Results. Finally, nine articles were included in the analysis, involving altogether 2,068 participants. In six of nine articles some improvement in viral load and/or symptoms duration was observed.

Conclusions. Our findings suggest evidence supporting the effectiveness of a combination therapy – oseltamivir combined with pimodivir, favipiravir, azithromycin, ribavirin and amantadine or clarithromycin and naproxen. These medicines may have potential clinical applications, however, further research involving larger patient population is required.

Keywords: oseltamivir, influenza, influenza virus, antiviral medicines

1. Introduction

Influenza virus belongs to Orthomyxoviridae family, which comprises RNA viruses (1) and are widely recognized as etiological factor of "seasonal flu". The most common symptoms include high fever lasting two to three days, chills, musculoskeletal pain, rhinorrhoea, sore throat and non-productive cough (2). Influenza-related complications are relatively common (3), particularly among paediatric and elderly, as well as patients with various comorbidities (4-7). According to World Health Organization data, approximately one billion cases of seasonal influenza occur annually worldwide, including 3–5 million cases of severe illness, resulting in an estimated 290 000 to 650 000 respiratory deaths every year.(8).

Moreover, virologists have identified four types of influenza viruses (A, B, C and D) and various subtypes according to the combinations of the proteins on the surface of the virus (1, 9). According to WHO reports, since October 2025 influenza A viruses have been dominating

among etiological factors of seasonal influenza (9, 10) and it is considered as a major health problem all over the world due to its substantial health and socioeconomic impact (11). A major challenge in influenza control is the high mutation rate of influenza viruses and their ability to undergo genetic reassortment with gene segments from different influenza viruses (1). Consequently, it seems to be remarkably difficult to keep pace with the development of vaccines targeting newly emerging strains, reliable diagnostic tests, including swab ones, and efficient antiviral treatments (12).

Clinical experience indicates that the most commonly used medicine for influenza is a selective neuraminidase inhibitor oseltamivir (13). On the other hand, some preclinical studies suggest that combination therapy involving antivirals or antibiotics may be more effective than oseltamivir monotherapy in the treatment of influenza (14, 15).

This study aims to contribute to the growing area of research by evaluating effectiveness of oseltamivir used either as monotherapy or in combination with other pharmacological agents in the treatment of influenza.

2. Research materials and methods

2.1 Participants

We defined our eligible population as adults (individuals aged ≥18 years old) with symptomatic and confirmed influenza infection diagnosed by a swab test and/or PCR test.

2.2 Procedure

We screened original articles evaluating oseltamivir treatment for influenza. An additional inclusion criteria was the availability of the full text in the English. Publications involving paediatric population or patients with previous severe diseases were excluded. The inclusion criteria were as follows: “adults”, “any gender”, “oseltamivir”, “oseltamivir monotherapy”, “publication year 2010 or later ”, “clinical trial”. Furthermore, the publications comprehend phrases as: “paediatric”, “children”, “neonatal”, “influenza vaccine”, “immune plasma” were excluded.

2.3 Data collection and analysis

After full-text analysis, we focused on following data: authors, year of publication, country in which the clinical trial was conducted, study population, applied treatment and results of research.

2.4 Statistical Software

Data were collected from PubMed, Web of Science and Google Scholar. Title and abstract screening was performed using Covidence software, and finally we included nine original articles.

3. Research results

After screening a total of 100 studies, we finally included nine studies involving 2,068 patients with confirmed influenza. Sample sizes ranged from 95 to 541 participants. Detailed information from each publication is summarized in the table below (Table 1). In all trials the control group received oseltamivir monotherapy in a standard dose alone or with placebo. A higher dose of oseltamivir (16), a monoclonal antibody MHAA4549A combined with oseltamivir (17) and zanamivir combined with oseltamivir (18) did not improve clinical or virological outcomes compared with standard oseltamivir therapy. In four of nine included articles, the investigated treatment reduced viral load more effectively than oseltamivir alone or with placebo (19-22). In addition, four studies reported improvement in influenza related symptoms, such as fever and sore throat, as well as reduced mortality and shorter duration of symptoms (21-24).

Table 1. Comparison of oseltamivir monotherapy and combination therapy.

	Authors	Publication year	Country	Study Population	Treatment	Results
1.	N. Lee et al. (16)	2013	China	157 adults hospitalized with influenza	Oseltamivir 150 mg twice daily for 5 days (higher dose than standard)	No significant difference in viral RNA negativity was found at day 5 between recipients of the 150 mg and 75 mg oseltamivir regimens (44.7% vs 40.2%). For influenza B, a trend toward faster viral clearance was observed with the higher-dose treatment (ANOVA: F=4.141, P=.051). There were found no significant difference in hospitalization duration, time to discontinuation of supplemental oxygen, or time to fever resolution between treatment groups in univariate analyses.
						Conclusion: Among the 155 oseltamivir-treated patients, there was no significant difference between recipients of 150 mg and 75 mg twice-daily oseltamivir.
2.	B. O'Neil et al. (23)	2022	USA	95 hospitalized adult patients with influenza A infection	Combination of oral pimodivir 600 mg plus oseltamivir 75 mg, both twice a day for 7 days	Time to influenza symptom resolution was numerically shorter with pimodivir (72.45 hours) than placebo (94.15 hours). There was a lower incidence of influenza related complications in the pimodivir group (7.9%) versus placebo group (15.6%). The estimated difference in viral load AUC of pimodivir plus

						oseltamivir treatment versus placebo plus oseltamivir treatment in the overall dataset was small (0.7 log10 vp/mL*day; 95% confidence interval [CI], −3.0 to 4.3).
						Conclusion: In this study, oral pimodivir plus oseltamivir showed a favourable safety profile. This preliminary exploratory efficacy trial demonstrated promising antiviral and clinical benefits in at-risk, hospitalized influenza A-infected patients.
3.	Y. Wang & G. Fan et al. (19)	2020	China	168 critically ill adults hospitalized with influenza	Oseltamivir at a dose of 75 mg twice daily for 10 days and either a favipiravir regimen of 1600 mg twice daily on day 1 followed by 600 mg twice daily on days 2–10 or a favipiravir regimen of 1800 mg twice daily on day 1 followed by 800 mg twice daily on days 2–10	Significantly lower proportions of patients with severe outcomes were observed according to the 7-category ordinal scale at day 7 (60.0% vs 63.3%; P = .0257) and day 14 (30.0% vs 48.5%; P = .0069) in the combination therapy cohort. The proportion of patients with undetectable viral RNA was significantly higher in the favipiravir plus oseltamivir group compared to the oseltamivir monotherapy group (10% vs 0.8% at day 2, 30% vs 5.5% at day 5, 45.0% vs 15.6% at day 7, and 67.5% vs 21.9% at day 10; all P < .01).

						Conclusion: Findings suggest that favipiravir and oseltamivir combination therapy may be associated with greater antiviral effects and faster clinical improvement in severe influenza. However, a double-blinded RCT is needed to establish the efficacy and safety of favipiravir and oseltamivir combination therapy compared to oseltamivir monotherapy.
4.	J. J. Lim et al. (17)	2020	USA	166 adults hospitalized with severe influenza	Single i.v. doses of 3,600 mg or 8,400 mg of a monoclonal antibody MHAA4549A and oseltamivir	Compared with placebo oseltamivir, MHAA4549A + oseltamivir did not significantly reduce the median time to removal of oxygen supplementation or positive-pressure ventilation, nor did the combination show statistically significant improvements in secondary efficacy endpoints. The median duration of hospitalization was not significantly different between the three treatment groups (7.65 and 6.69 days versus 8.95 days). Nasopharyngeal viral load showed no statistically significant differences between dose groups.
						Conclusion: The study demonstrated that MHAA4549A + oseltamivir treatment in patients hospitalized with severe influenza A virus infection does not improve clinical

						outcomes relative to placebo + oseltamivir.
5.	R. W. Finberg et al. (20)	2019	USA	223 adults with acute uncomplicated influenza A	An oral combination of pimodivir 600 mg and oseltamivir 75 mg in 10 doses at 12-hours intervals (twice a day)	The combination of pimodivir 600 mg plus oseltamivir 75 mg resulted in a significantly lower virus load AUC. The accelerated failure time model (expressed as the ratio of the time to resolution of 7 primary influenza symptoms in the pimodivir treatment groups as compared to the placebo group), adjusted for baseline composite score and stratum, showed trends but no statistically significant differences, with a faster time to resolution of influenza symptoms versus placebo observed with pimodivir 600 mg (13%) and pimodivir 600 mg plus oseltamivir 75 mg (17%).
						Conclusion: Pimodivir resulted in a significant and dose-dependent decrease in viral load, with the largest decrease in viral load observed for pimodivir 600 mg combined with oseltamivir 75 mg in; demonstrated trends in clinical improvement, and was well tolerated.
6.	I. F. N. Hung et al. (21)	2017	China	217 adults hospitalized for influenza A(H3N2) with pneumonia	A triple combination of clarithromycin 500 mg, naproxen 200 mg, and oseltamivir 75 mg	Combination treatment suppressed virus replication effectively within 24 hours. The reduction in virus titer was significantly higher in the combination treatment group than in

					twice daily for 2 days, followed by 3 days of oseltamivir 75 mg twice daily	the oseltamivir group between days 0 and 1 (1.45 vs 0.27 log10 M gene RNA copies/mL; P < .0001). The combination treatment was associated with lower 30-day mortality (P ¼ .01), less frequent high dependency unit admission (P ¼ .009), and shorter hospital stay (P < .0001). Multivariate analysis showed that combination treatment was the only independent factor associated with lower 30-day mortality (OR, 0.06; 95% CI, 0.004-0.94; P ¼ .04).
						Conclusion: The triple combination clarithromycin-naproxen-oseltamivir treatment reduced mortality, hospital stay, subsequent HDU admission, PSI, serial virus titer, and NIRV quasispecies without increased adverse effects.

7.	J. H. Beigel et al. (22)	2017	USA	394 adults with influenza A or B at increased risk of complications from influenza	Oseltamivir 75 mg, three capsules of over-encapsulated ribavirin 200 mg, and one capsule of over-encapsulated amantadine 100 mg, given twice daily for 5 days	Among the 454 participants in the efficacy population, the median duration of symptoms was 4.5 days in the combination arm vs 4.0 days in the oseltamivir arm (p = 0.21). No clinical symptomatic benefit could be demonstrated with the use of combination antivirals. Together with the quantitative reduction in viral load at day 3, the combination of oseltamivir, amantadine and ribavirin does indeed appear to decrease viral shedding relative to conventional monotherapy.
						Conclusions: It was demonstrated that the combination of oseltamivir, amantadine, and ribavirin had improved antiviral efficacy over oseltamivir alone in a population at risk for severe disease.

8.	H. Kakeya et al. (24)	2014	Japan	107 adults with symptomatic influenza from the Nagasaki University Hospital and 13 of its affiliated hospitals and clinics	Oral oseltamivir 75 mg every 12 h in combination with an extended-release formulation of single-dose oral azithromycin 2,000 mg for 5 days	Improvements in sore throat were observed more frequently on day 2 among patients in the combo-group than in the mono-group (p=0.05), similarly the combo-group showed a trend toward earlier resolution of fever (p=0.05 on day 2 and p=0.06 on day 5). No significant differences were observed between the2 groups in the resolution time of other influenza-related symptoms (headache, muscle or joint pain, heat sensation, feeling of fatigue, sore throat, nasal congestion and cough). No statistically significant differences were observed between the 2 groups in the expression of any of the inflammatory cytokines or chemokines on days 2 and 5.
						Conclusion: Although no statistically significant difference was observed in the expression levels of inflammatory cytokines and chemokines, the combination therapy showed a trend toward the earlier resolution of some symptoms.
9.	X. Duval et al. (18)	2010	France	541 adults 18 years old and older who consulted their general practitioner	Oseltamivir 75mg capsule for oral use twice a day plus inhaled zanamivir 10 mg by oral inhalation using the	The median time to resolution of illness in the enrolled patients was 3.5 days in the oseltamivir-zanamivir arm, 3.0 days in the oseltamivir monotherapy arm. In the ITT analysis, considering the 541

				within 36 hours of influenza symptoms onset	commercialized GlaxoSmithKline Diskhaler, twice a day	enrolled patients with positive influenza A rapid test, the proportion of patients with a RT-PCR < 200 cgeq/µl on day 2 of treatment was 52.6% in the oseltamivir-zanamivir arm, 62.5% in the oseltamivir monotherapy arm (p=0.055).
						Conclusion: In adults with seasonal influenza A (mainly H3N2) virus infection, the oseltamivir-zanamivir combination appeared less effective than oseltamivir monotherapy.

4. Discussion

Two of the selected publications focus on the combination of pimodivir and oseltamivir. O'Neil (23) reported that this combination resulted in significantly faster symptom relief and lower risk of complications, with only minor differences in viral control compared to monotherapy. In contrast, Finberg (20) demonstrated that viral load decreased more rapidly in the pimodivir plus oseltamivir group compared to the placebo group and however, although clinical outcomes were improved, the differences were not statistically significant. Data collected by the two researchers suggest that combination of drugs may be more efficient than oseltamivir alone, consequently further research is required to confirm these observations.

Hung (21) reported that a triple combination of clarithromycin, naproxen and oseltamivir significantly improved patient outcomes in cases of influenza complicated by pneumonia, both in terms of viral load reduction and clinical symptom improvement. Notably, mortality was significantly reduced. It can be said that this is a promising direction in the treatment of influenza complicated by pneumonia. Nevertheless, it is worth trying to include such treatment in a clinical practice and conducting further studies to demonstrate the effectiveness of triple therapy in a larger group of patients.

Another macrolide antibiotic evaluated in combination therapy is azithromycin, which was studied by Kakeya (24). However, the results were less conclusive than those observed in the previously described study. Although some symptoms of influenza were reduced and their

duration was shorter, no significant differences were found in cytokine levels. Therefore, the combination of azithromycin and oseltamivir may have potential clinical value, although further research will be needed.

Furthermore, the study performed by Beigel (22) demonstrated that the combination of oseltamivir, ribavirin and amantadine may also be beneficial for patients with influenza, resulting in faster viral shedding and a slightly shorter duration of symptoms. These findings may be used in everyday clinical practice, however, another studies are needed to confirm its effectiveness.

According to Lee (16), applying higher doses of oseltamivir do not improve clinical or virological outcomes, and therefore are not recommended. Similarly, the addition of the monoclonal antibody MHAA4549A (17) or zanamivir (18) to oseltamivir therapy did not demonstrate beneficial effects.

5. Conclusion

The findings of our study suggest that in general, combination treatment may be more effective than oseltamivir monotherapy in a standard dose. However, the differences between two compared groups were not substantial.

A major limitation of the included publications is a relatively small study population. Consequently, further research involving larger cohorts of participants is required.

Overall, given the continuous evolution of influenza viruses, the development of more effective therapeutic strategies remains an important research priority. Some of the combination therapies described above may represent promising alternatives to oseltamivir monotherapy and warrant further investigation.

Disclosure

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All authors have read and agreed to the published version of the manuscript.

Funding Statement:

The study did not receive any external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of Interest Statement:

The authors declare no conflicts of interest.

Ackonwledgements:

Not applicable.

Declaration of the use of generative AI and AI-assisted technologies in the writing process:

While preparing this work, the authors utilized OpenAI's Chat Generative Pre-trained Transformer to assist with correcting spelling, punctuation, grammar, and stylistic issues. Following the use of this tool, the authors reviewed and revised the content as necessary and take full responsibility for the final substance of the publication.

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