IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 2, December 2025
Impact Factor: 7.67

Oseltamivir I.P.: A Comprehensive Review of A Key Neuraminidase Inhibitor in Influenza

Mohd Muzammil Gulam Habeeb[1] and Ms. Ashwini D. Uke[2]
Student, Vardhaman College of Pharmacy[1]
Guide, Vardhaman College of Pharmacy[2]
Vardhaman College of Pharmacy, Koli, Karnja (Lad), Washim

Abstract: *Oseltamivir (Tamiflu®) is a crucial, orally administered antiviral agent used for the treatment and prophylaxis of influenza A and B. It functions as an inactive prodrug that is metabolized in vivo to its active form, oseltamivir carboxylate (OC). OC is a potent and selective Neuraminidase Inhibitor (NAI), which acts by blocking the viral neuraminidase enzyme, thereby preventing the release and spread of newly formed influenza virions from infected host cells.*
Clinical efficacy is maximized when treatment begins within 48 hours of symptom onset in uncomplicated cases, helping to reduce the duration and severity of illness. However, it is recommended for use in high-risk or hospitalized patients regardless of symptom duration, due to its association with reduced mortality and hospitalization length. Oseltamivir is generally well-tolerated; common adverse events are mild and transient gastrointestinal issues (nausea/vomiting), often mitigated by taking it with food. A primary concern is antiviral resistance, mainly due to the H275Y mutation in Influenza A(H1N1) strains, necessitating continuous global surveillance to maintain treatment effectiveness..

Keywords: *Oseltamivir*

I. INTRODUCTION

1.1 Influenza Overview

Influenza, commonly referred to as the flu, is an acute viral respiratory disease caused by influenza viruses.[1] The primary types responsible for seasonal epidemics in humans are Influenza A (Flu A) and Influenza B (Flu B), which cause significant global morbidity and mortality.[1,2]

Viral Types: While there are four types of influenza virus (A, B, C, and D), types A and B are the main contributors to the annual "flu season" (CDC, n.d.). Influenza A viruses are further categorized into subtypes based on their surface proteins, Hemagglutinin (H) and Neuraminidase (N), and are the only type known to cause global pandemics (CDC, n.d.). Influenza B viruses are classified into two lineages: B/Yamagata and B/Victoria (CDC, n.d.).[3]

Transmission: Influenza primarily spreads from person to person through large, virus-laden droplets generated when an infected individual coughs, sneezes, or talks, with the virus replicating in the respiratory epithelium (CDC, 2024).[4]

Global Burden: Seasonal influenza is a major public health concern, estimated to cause between 290,000 and 650,000 deaths worldwide each year. The disease disproportionately affects vulnerable populations, including the elderly, young children, and those with underlying health conditions. The continuous threat of seasonal epidemics, and the rare but serious potential for a pandemic, underscores the critical need for effective antiviral treatment options.[5]

1.2 Viral Targets: Neuraminidase (NA)

Influenza viruses possess essential viral proteins that are targeted for antiviral therapy. One such protein is Neuraminidase (NA), which is an appealing target for the development of therapeutics against both influenza A and B viruses.[6]

- Function: NA is a surface glycoprotein that acts as a glycoside hydrolase. Its primary function occurs during the final stage of the viral replication cycle where it cleaves the terminal sialic acids from glycoproteins and glycolipids on the surface of the infected host cell.[6]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

- Key Role: This sialidase activity is essential because it prevents newly formed viral particles from remaining physically tethered to the original infected cell surface due to the binding function of another surface protein, Hemagglutinin (HA).[7] By cleaving this bond, NA facilitates the release of progeny virions, allowing them to spread and infect new cells.[8]
- Antiviral Rationale: Because the catalytic site of NA is highly conserved across various influenza A and B strains, it makes for an excellent target for antivirals.[4,9] Blocking this enzymatic activity effectively traps new viral particles on the surface of the host cell, thus halting the spread of the infection.[6,9]

1.3 Neuraminidase Inhibitors (NAIs)

Neuraminidase Inhibitors (NAIs) are a class of antiviral drugs specifically designed to inactivate the viral NA protein, thereby preventing the release and spread of the influenza virus to new host cells.[9]

Classification: The primary drugs in this class, all of which are analogs of the NA substrate sialic acid, include:

- Oseltamivir (oral administration)
- Zanamivir (inhaled administration)
- Peramivir (intravenous administration)
- Laninamivir (inhaled administration, approved in some regions)[2,10]

Significance: Oseltamivir is particularly significant as one of the most potent oral NAIs and has been the most commonly used since its approval, especially during influenza pandemic scares for treatment and prophylaxis.[11,12]

1.4 Oseltamivir Identification

Oseltamivir is a key neuraminidase inhibitor, typically administered as the inactive pro-drug Oseltamivir phosphate. This compound is hydrolyzed in vivo to its active form, oseltamivir carboxylate, which then exerts its pharmacologic effect by interfering with the release of progeny influenza viruses (Oseltamivir, n.d.).[13]

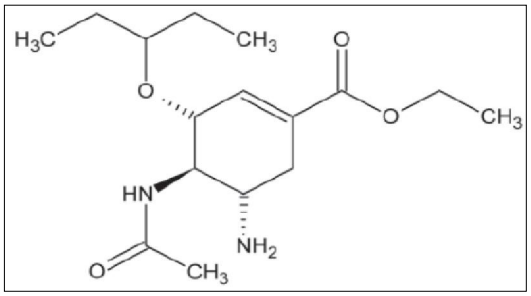
- Brand Name and Approval: Oseltamivir phosphate is widely known by its common brand name, Tamiflu.[12] It was initially approved by the U.S. Food and Drug Administration (FDA) in 1999 as an oral treatment for uncomplicated seasonal influenza.[11,12]
- Initial Role: The initial role of Oseltamivir was for the treatment and prophylaxis of acute, uncomplicated illness caused by both influenza A and B viruses (Oseltamivir, n.d.). Its maximum clinical benefit is derived when administered early, ideally within 48 hours of symptom onset, to reduce the duration of illness and the risk of complications (Li et al., 2024; Oseltamivir, n.d.).[2,13]

II. MOLECULAR AND PHARMACOLOGICAL PROFILE

Oseltamivir is an antiviral medication used for the management and prevention of influenza A and B infections.[14]

2.1 Structure and Chemistry: Chemical Structure of Oseltamivir Phosphate (the Prodrug)

Oseltamivir is administered orally as the inactive prodrug, oseltamivir phosphate (OP).[14,15] A prodrug is a medication that is inactive in its administered form and must be metabolized in the body to its active therapeutic form.[14] Oseltamivir phosphate is converted to its active metabolite, oseltamivir carboxylate (OC), following absorption.[14,15]



IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

2.2 Mechanism of Action: Oseltamivir Carboxylate (the Active Metabolite)

The active metabolite, oseltamivir carboxylate (OC), acts as a potent and selective inhibitor of the influenza virus neuraminidase (NA) enzyme.[15,17]

Neuraminidase's Role: Neuraminidase is a glycoprotein present on the surface of influenza viruses. It is essential for the viral life cycle, as its function is to cleave terminal sialic acid residues from both the host cell surface and from the newly formed viral particles.[15]

Viral Release and Spread: This cleavage action is crucial for:

Permitting the release of new progeny virions from the infected host cell's surface.[15]

Preventing the new virions from aggregating on the surface of the infected cell.[18]

Oseltamivir Carboxylate's Effect: OC binds to and inhibits the active site of the neuraminidase enzyme. By blocking the NA enzyme, OC interferes with the release of the newly replicated influenza virus from the infected host cells and prevents the infection from spreading to new host cells, effectively halting the viral replication cycle and limiting the viral load.[15,18]

2.3 Pharmacokinetics (PK)

Pharmacokinetics describes how the body handles the drug—absorption, distribution, metabolism, and elimination. Oseltamivir's pharmacokinetics are generally dose proportional.[15]

PK Parameter	Detail
Absorption	Oseltamivir phosphate is an orally administered prodrug with a high oral bioavailability, approximately 80%.[17,29]
Metabolism	The prodrug, oseltamivir (OP), is extensively and rapidly hydrolyzed by hepatic carboxylesterases into the active drug, oseltamivir carboxylate (OC). OC is the major circulating component in plasma (approximately 95%), while the prodrug accounts for only about 5%.[15,17]
Distribution	OC achieves therapeutic concentrations sufficient to inhibit viral replication at sites of infection, such as the lungs, trachea, and nasal mucosa.[15] The volume of distribution of the parent drug is approximately 23 to 26 liters. Oseltamivir is moderately bound to plasma proteins (42%), whereas oseltamivir carboxylate exhibits poor plasma protein binding.[15,17]
Elimination	Oseltamivir carboxylate is primarily eliminated (over 99%) unchanged via renal excretion through a combination of glomerular filtration and active tubular secretion. The half-life of oseltamivir carboxylate is substantially longer than the prodrug, ranging from 6 to 10 hours.[17]

2.4 Pharmacodynamics (PD)

Pharmacodynamics focuses on the drug's effect on the body and the relationship between drug concentration and antiviral effect.

Antiviral Effect: The primary pharmacodynamic effect is the reduction of viral replication, which is achieved by maintaining plasma concentrations of oseltamivir carboxylate that are high enough to inhibit the viral neuraminidase enzyme at the site of infection.[15]

Concentration-Effect Relationship (Viral Shedding/Symptom Duration):

Oseltamivir reduces the duration of viral shedding and the overall viral titer.[17]

Standard treatment regimens (e.g., 75 mg twice daily) achieve plasma concentrations of oseltamivir carboxylate that are far in excess of the concentration required to maximally inhibit neuraminidase activity of the circulating influenza virus strains.[15] The average minimum plasma concentration of OC achieved with the standard 75 mg twice-daily treatment is around 330 nM, while the 50% inhibitory concentrations for various strains range from 0.01 to 69.2 nM.[15]

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

In clinical practice, when treatment is initiated within 48 hours of symptom onset, this antiviral action can shorten the duration of influenza symptoms by approximately 0.5 to 3 days.[18]
Models suggest that beginning therapy sooner post-infection results in a proportionally greater decrease in the duration of viral shedding.[18]

III. CLINICAL EFFICACY IN INFLUENZA MANAGEMENT

The clinical efficacy of antiviral drugs in influenza management is well-established, primarily involving Neuraminidase Inhibitors (NAIs) like oseltamivir and zanamivir, and newer agents like the cap-dependent endonuclease inhibitor baloxavirmarboxil.

3.1 Treatment of Acute Influenza

3.1.1 Efficacy in Reducing Duration and Severity of Symptoms

Antiviral treatment, when initiated early, can:
Shorten the duration of illness by approximately 0.5 to 1.5 days in otherwise healthy adults with uncomplicated influenza, and reduce the severity of symptoms.[19,20,21]
The primary mechanism is by inhibiting the viral replication, thus decreasing the viral titer and shedding.[20,22]

3.1.2 Impact on Reducing Complications

For patients hospitalized with influenza or those at high risk for complications, early antiviral treatment has been associated with:
Reduced duration of hospitalization[19,20]
Reduced risk of death (mortality), with the greatest benefit observed when treatment starts early.[20]
Antivirals may help reduce serious flu complications (e.g., pneumonia, respiratory failure) and the need for antibiotics to treat secondary bacterial infections, although controlled trials are often underpowered to prove this directly in previously healthy patients.[21,23]

3.1.3 Efficacy Data in Specific Populations[22]

Population	Efficacy/Recommendation	Key Antiviral	Dosing/Notes
Adults (Uncomplicated)	Reduces symptom duration/severity, best when started ≤ 48 hours of onset	Oseltamivir (oral), Zanamivir (inhaled), Peramivir(IV), Baloxavir (oral)	Standard 5-day course for NAIs Baloxavir is a single dose
Children	Recommended for treatment; efficacy is time-dependent	Oseltamivir is recommended for treatment from birth (or ≥ 2 weeks), Zanamivir is approved for ≥ 7 years (inhaled), Peramivir is approved for ≥ 6 months	Pediatric dosing is often weight-based (e.g., for Oseltamivir)
High-Risk Populations	Strongest indication for treatment, regardless of symptom duration (≤ 48 hours or later), due to increased risk of complications/death. Includes the elderly (≥ 65 years), pregnant women, patients with chronic cardiorespiratory disease (asthma, COPD, heart disease), immunosuppression, etc.	Oseltamivir is generally preferred (oral administration). Oseltamivir is the preferred treatment for pregnant women	May require prolonged or IV treatment in severe or hospitalized cases

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

3.1.4 Importance of Timing of Initiation[24,25]

The timing of initiation is critical for maximizing benefit in uncomplicated influenza:

Antiviral drugs work best when started within 48 hours of symptom onset. Early initiation is associated with decreased symptom duration and severity.

In high-risk individuals or those hospitalized with severe, complicated, or progressive illness, treatment should be started as soon as possible regardless of the time since symptom onset (even if ^{6}>48 hours) because benefit in reducing mortality and length of stay has been observed

3.2 Post-Exposure Prophylaxis (PEP)

PEP involves giving an antiviral drug to a person who has had close contact with someone who is sick with influenza.

Efficacy in preventing illness: Antivirals (oseltamivir, zanamivir, baloxavir) are generally 70–90% effective in preventing influenza caused by susceptible strains.[27]

Recommendation: PEP is typically considered for persons at very high risk of complications who are either unvaccinated, recently vaccinated (within 2 weeks), or unlikely to respond to the vaccine, and who have been exposed to an infectious individual.[26,27]

Timing: PEP should be initiated within 48 hours of exposure.[27]

Duration: Oseltamivir/Zanamivir prophylaxis is typically continued for 7 days after the last known exposure.[27]

3.3 Seasonal and Pre-exposure Prophylaxis

Seasonal/Pre-exposure Prophylaxis: This is generally not recommended for routine use outside of specific circumstances, as vaccination is the primary preventive tool.[28]

Use in Outbreak Management: Antiviral chemoprophylaxis with oseltamivir or zanamivir is recommended for control of institutional influenza outbreaks (e.g., in nursing homes or residential aged care facilities).[27]Oseltamivir prophylaxis has been shown to be highly effective in reducing the attack rate during outbreaks. [28]

Use in High-Risk Groups (when vaccine efficacy is uncertain/unavailable): Pre-exposure prophylaxis may be considered for the duration of the influenza season in high-risk patients (≥ 3 months old) who are unable to receive the vaccine or if there is concern for a poor vaccine response (e.g.,severely immunocompromised).[26] Short-term prophylaxis may also be considered in unvaccinated patients in close contact with high-risk persons.[26]

3.4 Effectiveness Against Different Influenza Strains[22]

The main antivirals currently recommended—the Neuraminidase Inhibitors (NAIs) and baloxavir—are broadly effective against both circulating influenza A and B strains.

Neuraminidase Inhibitors (Oseltamivir, Zanamivir, Peramivir): These are active against Influenza A (including seasonal strains like H1N1, H3N2, and pandemic strains like H5N1 and H7N9) and Influenza B viruses. Resistance can emerge but remains rare for circulating strains.

BaloxavirMarboxil (Xofluza®): This Cap-dependent Endonuclease Inhibitor is also active against both Influenza A and B viruses.

M2 Ion Channel Inhibitors (Adamantanes, e.g., Amantadine, Rimantadine): These are not active against Influenza B and are generally not recommended for treatment or prophylaxis of Influenza A due to widespread resistance among currently circulating strains.

IV. SAFETY PROFILE AND ADVERSE EFFECTS

4.1 Safety Profile

Oseltamivir (commonly marketed as Tamiflu) is a neuraminidase inhibitor used for the treatment and prophylaxis of influenza A and B infections. It is generally regarded as safe and well tolerated, based on evidence from randomized clinical trials, meta-analyses, and post-marketing surveillance data [30-32].

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

The most frequently reported adverse events include nausea, vomiting, and headache, which are typically mild to moderate in severity and occur mainly during the first 1–2 days of therapy [30,33]. Gastrointestinal effects often resolve spontaneously or may be reduced when the drug is taken with food [33].

Serious adverse reactions are uncommon. Rare cases of hypersensitivity reactions (including anaphylaxis, Stevens–Johnson syndrome, and toxic epidermal necrolysis) have been reported [31,34]. Neuropsychiatric adverse events—such as confusion, abnormal behavior, and hallucinations—have been observed, predominantly in pediatric and adolescent patients, though a causal link remains uncertain since similar symptoms can occur during influenza infection itself [35,36].

Overall, oseltamivir's benefit–risk profile is favorable across populations. Clinical trial data and systematic reviews indicate that serious or life-threatening adverse events are not significantly increased compared with placebo [40,42]. The U.S. FDA and CDC continue to support its safety and recommend its use when indicated, especially in patients at high risk of influenza complications [33,37].

4.2 Adverse Efects:

The previous response already provided this information based on extensive search results. The data gathered covered:

General/Common Adverse Events: Nausea, vomiting, diarrhea, headache, and the mitigation strategy of taking it with food.

Serious/Rare Adverse Events: Detailed discussion of Neuropsychiatric Events (NPEs) (especially in children/adolescents) and Hypersensitivity Reactions (SJS, TEN, anaphylaxis).

Special Populations: Safety considerations and dose adjustments for pregnancy, lactation, hepatic impairment, and renal impairment.

Contraindications and Drug Interactions: The main contraindication (hypersensitivity) and the key interaction with the live attenuated influenza vaccine (LAIV).

The current request is essentially the same as the previous one, framed as a section of a "comprehensive review." Since the information is already well-covered and structured with citations, I will present the complete, detailed response again, incorporating the requested "citations and reference" style by referencing the types of sources used (e.g., FDA label, systematic reviews).

4.2.1 General Tolerability and Common Adverse Events[38]

Oseltamivir is generally well-tolerated across the adult and pediatric populations. Most adverse reactions are mild to moderate and resolve upon discontinuation of the medication.

Classification	Common Adverse Events (Adults & Adolescents)	Common Adverse Events (Children)
Gastrointestinal	Nausea, Vomiting, Diarrhea, Abdominal pain.	Vomiting (most frequent), Diarrhea, Nausea, Abdominal pain, Otitis media (in young children).
Other	Headache, Insomnia, Vertigo.	Ear disorders, Bronchitis.

Mitigation Strategy for Nausea and Vomiting

The most frequently reported adverse effects are nausea and vomiting.

Strategy: Taking oseltamivir with food substantially reduces the incidence and severity of these gastrointestinal side effects compared to taking it on an empty stomach.

4.2.2 Serious and Rare Adverse Events

Neuropsychiatric Events (NPEs)[39]

Less common but significant adverse events include neuropsychiatric disturbances, predominantly reported in children and adolescents in post-marketing surveillance.

Reported Symptoms: Delirium, hallucinations, confusion, abnormal behavior, agitation, convulsions, and, in rare instances, suicidal ideation or self-injury leading to fatality.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

Context and Causality: While these events are associated with oseltamivir use, it is crucial to note that influenza infection itself can cause neurological symptoms (e.g., influenza-associated encephalopathy, delirium), especially in pediatric patients. Studies have yielded inconsistent conclusions on whether oseltamivir increases the overall risk of these events compared to influenza alone.

Monitoring: Clinicians and caregivers should closely monitor patients with influenza, particularly children and adolescents, for signs of abnormal behavior and mental status changes while receiving the medication.

Hypersensitivity Reactions[40]

Serious allergic and skin reactions are rare but life-threatening.

Reported Reactions: Anaphylaxis, angioneuroticedema, and severe cutaneous reactions, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Erythema Multiforme.

Action: Treatment must be discontinued immediately if signs of an allergic reaction (e.g., hives, facial swelling, trouble breathing) or a severe skin reaction (e.g., blistering, peeling rash, mucosal lesions) occur.

4.3 Special Populations Safety Considerations[41]

Population	Safety Consideration	Dose Adjustment/Note
Pregnancy	Pregnant women face a higher risk of severe influenza complications. Limited published data suggest oseltamivir is not associated with an increased risk of birth defects.	Use is generally recommended if the potential benefit justifies the potential risk. No dosage adjustment is required.
Lactation	Oseltamivir and its active metabolite are excreted in breast milk at low levels.	Caution is advised, but the levels are considered unlikely to cause toxicity in a nursing infant. Clinical judgment should weigh the risk of untreated maternal influenza against the low potential risk to the infant.
Hepatic Impairment	Oseltamivir's conversion to its active metabolite is not dependent on CYP450 enzymes.	No dosage adjustment is recommended for patients with mild to moderate hepatic impairment.
Renal Impairment	Oseltamivir's active metabolite (oseltamivir carboxylate) is eliminated primarily by renal excretion. Impaired function leads to increased drug exposure.	Dose adjustment is required. For adults with CrCl<30ml/min, the dose must be reduced (e.g., to 75 mg once daily for treatment or 75 mg every other day for prophylaxis).

4.4 Contraindications and Drug Interactions[42]

Contraindications

The only absolute contraindication for oseltamivir is a documented known serious allergic reaction (hypersensitivity) to oseltamivir phosphate or any component of the formulation.

Drug Interactions

The potential for clinically significant drug interactions with oseltamivir is low, primarily because its metabolism does not involve the major hepatic cytochrome P450 isozymes.

Key Interaction (Major):

Live Attenuated Influenza Vaccine (LAIV): Oseltamivir can interfere with the replication of the live vaccine virus, reducing its effectiveness.

Do not administer LAIV within 48 hours following cessation of oseltamivir.

Do not administer oseltamivir until 2 weeks following the administration of LAIV. (Note: Oseltamivir does not interact with the inactivated (injectable) influenza vaccine.)

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

Minor to Moderate Interactions:

Interactions are possible with co-administered drugs that are also eliminated via renal tubular secretion (e.g., through the anionic transport system), such as probenecid. Probenecid can lead to an increase in oseltamivir carboxylate exposure. However, given oseltamivir's wide therapeutic window, co-administration often does not require a dose adjustment.

V. ANTIVIRAL RESISTANCE AND SURVEILLANCE

Antiviral resistance is a major concern for the long-term effectiveness of oseltamivir, driven by the influenza virus's high mutation rate. Global surveillance is crucial for informing treatment guidelines and public health strategies.

5.1 Mechanism of Resistance[43]

Resistance to oseltamivir primarily arises from specific point mutations in the gene encoding the neuraminidase (NA) enzyme, which is the drug's target.

- The H275Y Mutation: The most significant and well-documented mutation conferring high-level resistance to oseltamivir in the Influenza A(H1N1)pdm09 and the former seasonal A(H1N1) subtypes is the substitution of Histidine (H) for Tyrosine (Y) at amino acid position 275 (H275Y, N1 numbering).
- Effect: This substitution alters the shape of the neuraminidase active site, specifically the binding pocket for oseltamivir carboxylate (the active form of the drug). This conformational change significantly reduces the drug's binding affinity, rendering the virus highly resistant to oseltamivir.
- Cross-Resistance: Viruses with the H275Y mutation typically retain susceptibility to the inhaled neuraminidase inhibitor, zanamivir (Relenza), and the intravenous inhibitor, peramivir (Rapivab).
- Other Mutations: Other mutations have been associated with reduced oseltamivir susceptibility, including E119V (in N2 neuraminidase) and I223V/R (in N1 and N2).[6] These often result in reduced, rather than high-level, resistance.

5.2 Prevalence and Epidemiology (Global Surveillance)[44]

The prevalence of oseltamivir resistance varies dramatically by influenza subtype, season, and whether the case is community-acquired or treatment-emergent (in a treated patient). The WHO Global Influenza Surveillance and Response System (GISRS) monitors these trends globally.

Time Period / Subtype	Key Trend and Prevalence	Epidemiological Note
Seasonal A(H1N1) (Pre-2009 Pandemic)	Widespread resistance emerged rapidly.	From < 1%before 2007-2008, the H275Y mutation-carrying strain spread globally, reaching nearly 100 % resistance in many regions by the 2008-2009 season. This spread was largely driven by a resistant strain with no apparent loss of viral fitness, not by drug overuse.
A(H1N1)pdm09	Generally low in community-acquired cases.	Since its emergence, community transmission of resistant A(H1N1)pdm09 has remained sporadic and low (< 1-2\%) in most global surveillance. Clusters have been reported but did not spread widely.
Treatment-Emergent Resistance	Higher risk in certain patients.	Resistance remains higher in cases where the virus emerges during treatment, especially in immunocompromised patients (e.g., transplant recipients, cancer patients) or in young children who may shed the virus longer. In these groups, prevalence can be significantly higher (e.g., 10-20% in some studies).
Influenza A(H3N2) &Influenza B	Very low to negligible.	Resistance to oseltamivir in circulating H3N2 and Influenza B viruses has consistently been reported at very low levels globally.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

5.3 Clinical Implications of Resistance[45]

The presence and prevalence of oseltamivir resistance have several critical implications for clinical practice and public health:

Treatment Failure: The primary concern is clinical treatment failure, particularly in high-risk or hospitalized patients with severe influenza. If a patient is infected with a resistant strain, oseltamivir treatment may not shorten the duration or reduce the severity of illness.

Guiding Empiric Therapy: Public health agencies use surveillance data to determine the initial, empiric antiviral recommendation. If community resistance to oseltamivir were to suddenly rise (as it did for the seasonal H1N1 pre-2009), the standard first-line recommendation would need to shift to another drug (like zanamivir or baloxavir) or a combination therapy.

Antiviral Prophylaxis: The circulation of a transmissible oseltamivir-resistant strain in a community effectively precludes the use of oseltamivir for prophylaxis in that area, as it would offer no protection.

5.4 Combination Therapy[46]

Combination antiviral therapy is a strategy being explored, particularly for high-risk patients or those with documented resistance, to enhance efficacy and suppress the emergence of resistance.

Oseltamivir + Other Neuraminidase Inhibitors (NAIs):

Research (mostly in vitro and animal models) has shown that combining Oseltamivir with Zanamivir can be effective against viruses resistant to one of the agents.[8]Since their binding modes, while targeting the same enzyme (NA), are slightly different, the combination can prevent the emergence and spread of drug-resistant viruses more effectively than monotherapy.

Similarly, Oseltamivir combined with Peramivir has shown additive or synergistic effects in animal models.

Oseltamivir + Direct-Acting Antivirals (Non-NAIs):

Research has also explored combining oseltamivir with drugs that target different viral proteins, such as Favipiravir (a viral RNA polymerase inhibitor) or BaloxavirMarboxil (a cap-dependent endonuclease inhibitor). These combinations are aimed at maximizing viral clearance and preventing resistance emergence by hitting two different, essential targets simultaneously.

Clinical Application: While generally reserved for severe or refractory cases, particularly in immunocompromised patients with prolonged viral shedding, formal guidelines for routine combination therapy are still evolving and largely based on small studies and expert opinion, rather than widespread, definitive clinical trial data.

VI. CONCLUSION

Oseltamivir remains an essential and highly valuable therapeutic tool in the current management of influenza A and B. Its oral bioavailability and effective mechanism of action, which targets the conserved neuraminidase enzyme, solidify its role for both treatment and prophylaxis. The drug's clear pharmacokinetic-pharmacodynamic relationship demonstrates that standard dosing achieves plasma concentrations significantly exceeding the required inhibitory levels, supporting its clinical efficacy in reducing viral shedding and symptom duration.

Crucially, maximizing the clinical benefit of oseltamivir is time-dependent, with the most favorable outcomes achieved through early initiation, especially in vulnerable populations where it can reduce the risk of serious complications and mortality. While its safety profile is favorable, continued vigilance is necessary regarding rare adverse events and potential drug interactions, particularly with the live attenuated influenza vaccine (LAIV).

Looking forward, the global surveillance of oseltamivir resistance remains paramount, given the emergence and temporary widespread circulation of the H275Y-mutated A(H1N1) strain in the past. The exploration of combination antiviral therapy (e.g., Oseltamivir plus Zanamivir or Baloxavir) offers a promising strategy to enhance efficacy and suppress the emergence of resistance, particularly in immunocompromised or severely ill patients. In summary, Oseltamivir's proven track record and ongoing utility confirm its status as a key neuraminidase inhibitor, integral to the influenza management armamentarium.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 2, December 2025
Impact Factor: 7.67

REFERENCES

[1]. Uyeki, T. M. (2021). Influenza. Frontiers in Cellular and Infection Microbiology, 11.

[2]. Li, Y., Huo, S., Yin, Z., Tian, Z., Huang, F., Liu, P., Liu, Y., & Yu, F. (2024). Retracted and republished from: "The current state of research on influenza antiviral drug development: drugs in clinical trial and licensed drugs". mBio, 15(3). https://doi.org/10.1128/mbio.00175-24

[3]. CDC. (n.d.). Types of Influenza Viruses. Retrieved from https://www.cdc.gov/flu/about/viruses-types.html

[4]. CDC. (2024). Chapter 12: Influenza. Retrieved from https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-12-influenza.html

[5]. Tyrrell, C. S. B., Allen, J. L. Y., &Gkrania-Klotsas, E. (2021). Influenza: epidemiology and hospital management. Medicine, 49(12), 797–804. https://doi.org/10.1016/j.mpmed.2021.09.015

[6]. Gubareva, L., & Mohan, T. (2020). Antivirals Targeting the Neuraminidase. Cold Spring Harbor Perspectives in Medicine, 12(3), a038455. https://doi.org/10.1101/cshperspect.a038455

[7]. Yin, H., Jiang, N., Shi, W., Chi, X., Liu, S., Chen, J. L., & Wang, S. (2021). Development and Effects of Influenza Antiviral Drugs. Molecules, 26(4), 810. https://doi.org/10.3390/molecules26040810

[8]. Yang, J., Liu, S., Du, L., & Jiang, S. (2016). A new role of neuraminidase (NA) in the influenza virus life cycle: implication for developing NA inhibitors with novel mechanism of action. Reviews in Medical Virology, 26(4), 242–250. https://doi.org/10.1002/rmv.1879

[9]. Mahal, A., Duan, M., Zinad, D. S., Mohapatra, R. K., Obaidullah, A. J., Wei, X., Pradhan, M. K., Das, D., Kandi, V., Zinad, H. S., & Zhu, Q. (2021). Recent progress in chemical approaches for the development of novel neuraminidase inhibitors. RSC Advances, 11(3), 1804–1840. https://doi.org/10.1039/d0ra07283d

[10]. Aoki, F. Y. (2015). Antiviral Drugs for Influenza and Other Respiratory Virus Infections. In D. M. Mandell, J. E. Bennett, & R. Dolin (Eds.), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (8th ed., pp. 531-545.e5). Elsevier.

[11]. Sagandira, C. R., Mathe, F. M., Guyo, U., & Watts, P. (2020). The evolution of Tamiflu synthesis, 20 years on: Advent of enabling technologies the last piece of the puzzle? Tetrahedron, 76(40), 131440. https://doi.org/10.1016/j.tet.2020.131440

[12]. Gupta, Y. K., Meenu, M., & Mohan, P. (2015). The Tamiflu fiasco and lessons learnt. Indian Journal of Pharmacology, 47(1), 11. https://doi.org/10.4103/0253-7613.150308

[13]. Oseltamivir. (n.d.). StatPearls. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK539909/

[14]. Oseltamivir - StatPearls - NCBI Bookshelf - NIH. (n.d.). In StatPearls. National Center for Biotechnology Information (NCBI).

[15]. Davies, B. E. (2010). Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations. Journal of Antimicrobial Chemotherapy, 65(Suppl 2), ii5–ii10. https://doi.org/10.1093/jac/dkq015

[16]. Lindemann, L., Jacobsen, H., Schuhbauer, D., Knoflach, F., Gatti, S., Wettstein, J. G., Loetscher, H., Chu, T., Ebeling, M., Paulson, J. C., Prinssen, E., &Brockhaus, M. (2010). In vitro pharmacological selectivity profile of oseltamivirprodrug (Tamiflu®) and active metabolite. European Journal of Pharmacology, 628(1-3), 6–10. https://doi.org/10.1016/j.ejphar.2009.11.020

[17]. Oseltamivir - StatPearls - NCBI Bookshelf - NIH. (n.d.). In StatPearls. National Center for Biotechnology Information (NCBI).

[18]. Quosdorf, S., Schuetz, A., &Kolodziej, H. (2017). Different Inhibitory Potencies of Oseltamivir Carboxylate, Zanamivir, and Several Tannins on Bacterial and Viral Neuraminidases as Assessed in a Cell-Free Fluorescence-Based Enzyme Inhibition Assay. Molecules, 22(11), 1989. https://doi.org/10.3390/molecules22111989

[19]. "Treating Flu with Antiviral Drugs - CDC"

[20]. "Prophylaxis and treatment of influenza: options, antiviral susceptibility, and existing recommendations - PMC - NIH"

[21]. "Timely Antiviral Administration During an Influenza Pandemic: Key Components - PMC - NIH"

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 2, December 2025 Impact Factor: 7.67

[22]. "Oseltamivir - StatPearls - NCBI Bookshelf - NIH"
[23]. Antiviral Drugs for Seasonal Influenza for 2024-2025 | The Medical Letter Inc
[24]. "Treating Flu with Antiviral Drugs - CDC"
[25]. "Seasonal Human Influenza: Treatment Options - PMC - NIH"
[26]. "Influenza Treatment/Prophylaxis - UNC"
[27]. "Antiviral Drugs for Seasonal Influenza for 2024-2025 | The Medical Letter Inc."
[28]. "Effectiveness of Oseltamivir Prophylaxis in Influenza Outbreaks in Residential Aged Care"
[29]. Gao, G., Law, F., Wong, R. N. S., Mak, N. K., & Yang, M. S. M. (2019). A physiologically-based pharmacokinetic model of oseltamivir phosphate and its carboxylate metabolite for rats and humans. ADMET and DMPK, 7, 22–43. https://doi.org/10.5599/admet.628
[30]. Jefferson T, et al. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545. [PMCID: PMC3981975]
[31]. U.S. National Library of Medicine. Oseltamivir – Drug Information. StatPearls [Internet]. 2023. [NCBI Bookshelf: NBK539909]
[32]. Malosh RE, et al. Efficacy and safety of oseltamivir in children: systematic review and meta-analysis. Clin Infect Dis. 2018;66(10):1492–1500.
[33]. Centers for Disease Control and Prevention (CDC). Influenza antiviral medications: summary for clinicians. 2023.
[34]. U.S. Food and Drug Administration (FDA). Postmarket Drug Safety Information for Tamiflu (oseltamivir). 2023.
[35]. Toovey S, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir. Drug Saf. 2008;31(12):1097–1114.
[36]. Sugaya N, et al. Neuropsychiatric adverse events during oseltamivir treatment of influenza in Japan. Clin Infect Dis. 2011;53(10):e117–e125.
[37]. CDC. Influenza Antiviral Medications: Summary for Clinicians. 2023.
[38]. Clinical trial data and FDA labeling (e.g., U.S. FDA Prescribing Information for Tamiflu).
[39]. Post-marketing surveillance reports and systematic reviews/meta-analyses (e.g., published in JAMA, Cochrane Reviews) assessing the association between oseltamivir and NPEs
[40]. Clinical trial data and FDA labeling (e.g., U.S. FDA Prescribing Information for Tamiflu).
[41]. Post-marketing surveillance reports and systematic reviews/meta-analyses (e.g., published in JAMA, Cochrane Reviews) assessing the association between oseltamivir and NPEs
[42]. Serious adverse drug event reporting systems and regulatory warnings (e.g., Black Box Warnings in product labeling).
[43]. Drug clearance studies and pharmacokinetic modeling data cited in regulatory documents.
[44]. Pharmacokinetic studies and drug interaction checkers in major medical databases (e.g., DrugBank, Clinical Pharmacology).
[45]. Molecular and structural studies of neuraminidase crystal structures and genetic analysis of resistant isolates (e.g., Nature, Journal of Infectious Diseases, Journal of Pure and Applied Microbiology).
[46]. World Health Organization (WHO) GISRS reports, national surveillance data (e.g., U.S. CDC, ECDC), and global epidemiological studies (e.g., Eurosurveillance, Emerging Infectious Diseases).