Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial

Christopher C Butler, Alike W van der Velden, Emily Bongard, Benjamin R Saville, Jane Holmes, Samuel Coenen, Johanna Cook, Nick A Francis, Roger J Lewis, Maciek Godycki-Cwirko, Carl Llor, Sławomir Chlabicz, Christos Lionis, Bohumil Seifert, Pär-Daniel Sundvall, Annelies Colliers, Rune Aabenhus, Lars Bjerrum, Nicolay Jonassen Harbin, Morten Lindbæk, Dominik Glinz, Heiner C Bucher, Bernadett Kovács, Ruta Radzeviciene Jurgute, Pia Touboul Lundgren, Paul Little, Andrew W Murphy, An De Sutter, Peter Openshaw, Menno D de Jong, Jason T Connor, Veerle Matheeussen, Margareta Ieven, Herman Goossens, Theo J Verheij

RobotReviewer report

Risk of bias table

trial	design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Butler CC, 2019	RCT	+	+	?	+

Trial summaries

n	Participants	Interventions	Outcomes	punchline	finding
?? ?	primary care, patients with influenza-like illness	Oseltamivir plus usual care versus usual care		Regarding harms, we did not identify meaningful differences in patient-reported repeat visits with health care services, hospitalisations, or serious adverse events, but found evidence for increased burden of vomiting or nausea in the usual care plus oseltamivir group, which is a common side-effect of oseltamivir.	‚Äï no diff

Characteristics of studies

Butler CC, 2019

Population

1. Exclusion criteria included: chronic renal failure; substantial impaired immunity (eg, long-term oral steroids, chemotherapy, or immune disorder); patients who should be prescribed immediate antiviral treatment or immediate hospitalisation in the opinion of the responsible clinician; allergy to oseltamivir; scheduled elective surgery or other procedures requiring general Research in context Evidence before this study
2. Stratified block randomisation was implemented, with random blocks of two, four, and six participants and stratification by age (<12, 12-<65, and ‚â•65 years), overall severity of influenza- like illness (rated by the responsible clinician as mild, moderate, or severe), any relevant comorbidity (yes or no for heart disease, diabetes, chronic respiratory condition, hepatic, haematological, neuro logical, or neurodev-elopmental condition, stroke or transient ischaemic attack, or overnight hospital stay in previous year), and previous duration of symptoms since onset (‚â§48 h or >48-72 h, based on recommendations that oseltamivir should be started within 48 h of

	symptom onset). 3. anaesthesia during the subsequent 2 weeks; life expec- tancy estimate of less than 6 months; severe hepatic impairment; unable to be randomised within 72 h after onset of symptoms; requirement for any live viral vaccine in the next 7 days; and, in some jurisdictions, pregnant, lactating, or breastfeeding women.
Intervention	1. Procedures Adults and children weighing more than 40 kg who were assigned to the usual care plus oseltamivir and able to swallow capsules were given 75 mg oral oseltamivir twice daily for 5 days. 2. Randomisation and masking Participants were randomly assigned at the point of care, using a remote online electronic data capture system (Research Online 2), to either usual primary care according to general practitioners' normal preferences or oseltamivir plus usual care in a 1:1 ratio. 3. For children younger than 13 years, oseltamivir was given in oral suspension according to weight (children weighing 10-15 kg received 30 mg, >15-23 kg received 45 mg, >
Outcomes	1. Influenza-like illness was defined as a sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, or running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills, or tiredness), with symptom duration of 72 h or less during a seasonal influenza epidemic. 2. Secondary outcomes were cost-effectiveness of adding antiviral treatment to usual primary care (to be reported separately), incidence of hospital admissions, compli cations related to influenza-like illness, repeat attendance in general practice, time to alleviation of symptoms of influenza-like illness, incidence of new or worsening symptoms, time to initial reduction in severity of symptoms, use of additional symptomatic and prescribed medication, including antibiotic, transmission of infection within household, and self-management of symptoms of influenza-like illness. 3. anaesthesia during the subsequent 2 weeks; life expec- tancy estimate of less than 6 months; severe hepatic impairment; unable to be randomised within 72 h after onset of symptoms; requirement for any live viral vaccine in the next 7 days; and, in some jurisdictions, pregnant, lactating, or breastfeeding women.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Randomisation and masking Participants were randomly assigned at the point of care, using a remote online electronic data capture system (Research Online 2), to either usual primary care according to general practitioners' normal preferences or oseltamivir plus usual care in a 1:1 ratio. 2. Neither criterion was met, so a 1:1 randomisation ratio was maintained throughout the trial. 3. The Fast Track Diagnostics Respiratory Pathogens 21 plus real-time PCR assay (Fast Track Diagnostics, Luxembourg) was used to determine the aetiology, including influenza A and B status after each season, or after study completion, but results were not available for clinicians to inform management.
Allocation concealment	low	1. Randomisation and masking Participants were randomly assigned at the point of care, using a remote online electronic data capture system (Research Online 2), to either usual primary care according to general practitioners' normal preferences or oseltamivir plus usual care in a 1:1 ratio. 2. This was an open-label study, so no placebo was used and drugs were not masked. 3. The Fast Track Diagnostics Respiratory Pathogens 21 plus real-time PCR assay (Fast Track Diagnostics, Luxembourg) was used to

		determine the aetiology, including influenza A and B status after each season, or after study completion, but results were not available for clinicians to inform management.
Blinding of participants and personnel	high/ unclear	1. This was an open-label study, so no placebo was used and drugs were not masked. 2. Contributors CCB and TJV were co-chief investigators of this trial and act as guarantors of the study in its entirety. 3. BRS, JH, RJL, and JTC were the trial statisticians.
Blinding of outcome assessment	low	1. This was an open-label study, so no placebo was used and drugs were not masked. 2. The Fast Track Diagnostics Respiratory Pathogens 21 plus real-time PCR assay (Fast Track Diagnostics, Luxembourg) was used to determine the aetiology, including influenza A and B status after each season, or after study completion, but results were not available for clinicians to inform management. 3. Randomisation and masking Participants were randomly assigned at the point of care, using a remote online electronic data capture system (Research Online 2), to either usual primary care according to general practitioners' normal preferences or oseltamivir plus usual care in a 1:1 ratio.

References

1. Butler CC et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial BMJ 2019. 10217; 42-52 PMID: 19843565