Testing treatment of Tamiflu: a perspective from *Chevidence*

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Disclosure of interests

- Methodologist, Evidence-based Medicine Center of Lanzhou University
- Director, the Chinese GRADE Center
- Member, GIN(Guideline International Network) Asia Steering Group
- Co-Director, WHO Collaborating Centre for Guideline Implementation and Knowledge Translation
- **I have no conflicts of interest related to the presentation**

2017 flu season in China

2018

中华人民共和国国家卫生健康委员会
National Health Commission of the People's Republic of China

流行性感冒诊疗方案（2018年版）

流行性感冒（以下简称流感）是由流感病毒引起的一种急性呼吸道传染病，在世界范围内引起暴发和流行。

流感起病急，虽然大多为自限性，但部分因出现肺炎等并发症可发展至重症流感，少数重症病例病情进展快，可因急性呼吸窘迫综合征(ARDS)和/或多脏器衰竭而死亡。重症流感主要发生在老年人、年幼儿童、孕产妇或有慢性基础疾病者等高危人群，亦可发生在一般人群。

2017年入冬以来，我国南北方省份流感活动水平上升较快，当前处于冬季流感流行高峰水平。全国流感监测结果显示，流感样病例就诊百分比和流感病毒检测阳性率均显著高于过去三年同期水平，流感活动水平仍呈现上升态势，本次冬季流感活动强度要强于往年。

为进一步规范和加强流感的临床管理，减少重症流感发生、降低病死率，在《甲型H1N1流感诊疗方案（2009年第三版）》和《流行性感冒诊断与治疗指南（2011年版）》的基础上，结合近期国内外研究成果及我国既往流感诊疗经验，制定本诊疗方案。

一、病原学

流感病毒属于正粘病毒科，为RNA病毒。根据核蛋白和基质蛋白分为甲、乙、丙、丁四型。

目前感染人的主要是甲型流感病毒中的H1N1、H3N2亚型

短病程、减少并发症也可以抗病毒治疗。

2. 抗流感病毒药物

神经氨酸酶抑制剂（NAI）对甲型、乙型流感均有效。

（1）奥司他韦：成人剂量每次75mg，每日2次，疗程5天，重症病例剂量可加倍，疗程可延长。肾功能不全者要根据肾功能调整剂量。1岁及以上年龄的儿童应根据体重给药：体重不足15Kg者，予30mg每日2次；体重15～23Kg者，予45mg每日2次；体重23～40Kg者，予60mg每日2次；体重大于40Kg者，予75mg每日2次。对于吞咽胶囊有困难的儿童，可选用奥司他韦颗粒剂。对用药过程中无效或病情加重的患者，要注意是否出现耐药。

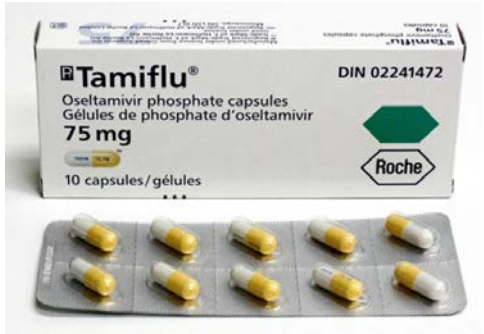
（2）扎那米韦：适用于于成人及7岁以上青少年，用法：每日2次，间隔12小时；每次10mg（分两次吸入）。但吸入剂不建议用于重症或有并发症的患者。

（3）帕拉米韦：成人用量为300～600mg，小于30d新生儿6mg/kg，31-90d婴儿8mg/kg，91d-17岁儿童10mg/kg，静脉滴注，每日1次，1～5天，重症病例疗程可适当延长。目前临床应用数据有限，应严密观察不良反应。

离子通道M2阻滞剂金刚烷胺和金刚乙胺仅对甲型流感病毒有效，但目前监测资料显示甲型流感病毒对其耐药，不建议使用。

（四）重症病例的治疗

治疗原则：积极治疗原发病，防治并发症，并进行有效



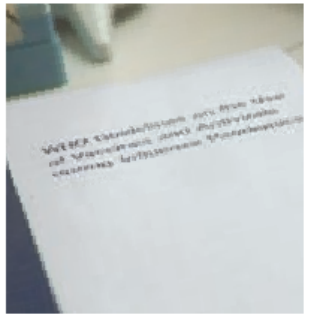
Tamiflu and conspiracies

bmj.com

- See a video to accompany this investigation at http://bit.ly/c3eEh3
- Read Deborah Cohen's previous investigation—Complications: tracking down the data on oseltamivir (*BMJ* 2009;339:b5387)

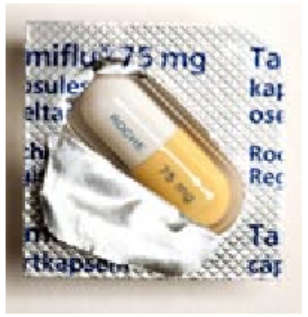
WHO and the pandemic flu "conspiracies"

Key scientists advising the World Health Organization on planning for an influenza pandemic had done paid work for pharmaceutical firms that stood to gain from the guidance they wrote. These conflicts of interest have never been publicly disclosed by WHO. **Deborah Cohen** and **Philip Carter** investigate



The 2004 WHO pandemic guidelines advised governments to stockpile antivirals. No conflict of interest statements were published

A year ago this week, WHO's director general, Margaret Chan, declared that an influenza pandemic had broken out



Billions of dollars' worth of antivirals, such as oseltamivir and zanamivir, have been stockpiled on WHO's recommendation

Speaking at the Centers for Disease Control this year, Dr Chan dismissed allegations of industry influence on WHO as "conspiracies"

Paul Flynn MP said there had been a distortion of public health priorities and a waste of public money

2012

REVIEW | Annals of Internal Medicine

Antivirals for Treatment of Influenza

A Systematic Review and Meta-analysis of Observational Studies

Jonathan Hsu, BHSc; Nancy Santesso, MLIS, RD; Reem Mustafa, MD, MPH; Jan Brozek, MD; Yao Long Chen, MSc; Jessica P. Hopkins, MD, MHSc; Adrienne Cheung, BHSc; Gayane Hovhannisyan, MD; Liudmila Ivanova, MD, MPH, MSc; Signe A. Flottorp, MD, PhD; Ingvil Sæterdal, MSc, PhD; Arthur D. Wong, BHSc; Jinhui Tian, MSc; Timothy M. Uyeki, MD, MPH, MPP; Elie A. Akl, MD, MPH, PhD; Pablo Alonso-Coello, MD, PhD; Fiona Smaill, MB, ChB, MSc; and Holger J. Schünemann, MD, MSc, PhD

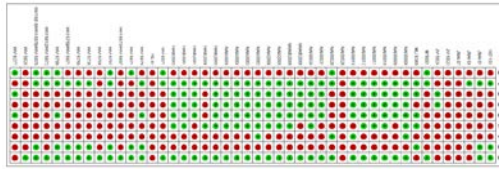
Table 1. GRADE Evidence Profile for Oral Oseltamivir Versus No Antiviral Therapy

Outcome	Quality Assessment		Summary of Findings		
	Participants (Studies), *n**	Overall Quality of Evidence	Study Event Rates, *n/N (%)*		Relative Effect (95% CI)
			No Antiviral Treatment	Oseltamivir	
Mortality	681 (3) 1557 (9)	Low† Very low due to risk of bias†‡	59/242 (24.4) 61/320 (19.1)	31/439 (7.1) 228/1237 (18.4)	Adjusted OR, 0.23 (0.13–0.43) OR, 0.51 (0.23–1.14)§
Hospitalization	150 710 (4) 242 762 (6)	Low‖ Very low due to risk of bias‡‖	1238/100 585 (1.2) 1738/146 410 (1.2)	431/50 125 (0.86) 1086/96 352 (1.1)	Adjusted OR, 0.75 (0.66–0.89) OR, 0.75 (0.66–0.86)

2014

Cochrane Library

Cochrane Database of Systematic Reviews



Neuraminidase inhibitors for preventing and treating influenza in adults and children (Review)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya IJ, Mahtani KR, Nunan D, Howick J, Heneghan CJ

Authors' conclusions

Oseltamivir and zanamivir have small, non-specific effects on reducing the time to alleviation of influenza symptoms in adults, but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir compared to oseltamivir. The balance between benefits and harms should be considered when making decisions about use of both NIs for either the prophylaxis or treatment of influenza. The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence.

2014-2015

Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data

Interpretation We advocate early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

Funding F Hoffmann-La Roche.

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Interpretation Our findings show that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting.

Funding Multiparty Group for Advice on Science (MUGAS) foundation.

2016

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 42 MAY 2016
ISSN 1366-5278

NHS
National Institute for Health Research

Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data

Carl J Heneghan, Igho Onakpoya, Mark A Jones, Peter Doshi, Chris B Del Mar, Rokuro Hama, Matthew J Thompson, Elizabeth A Spencer, Kamal R Mahtani, David Nunan, Jeremy Howick and Tom Jefferson

Funding: The National Institute for Health Research Health Technology Assessment programme.

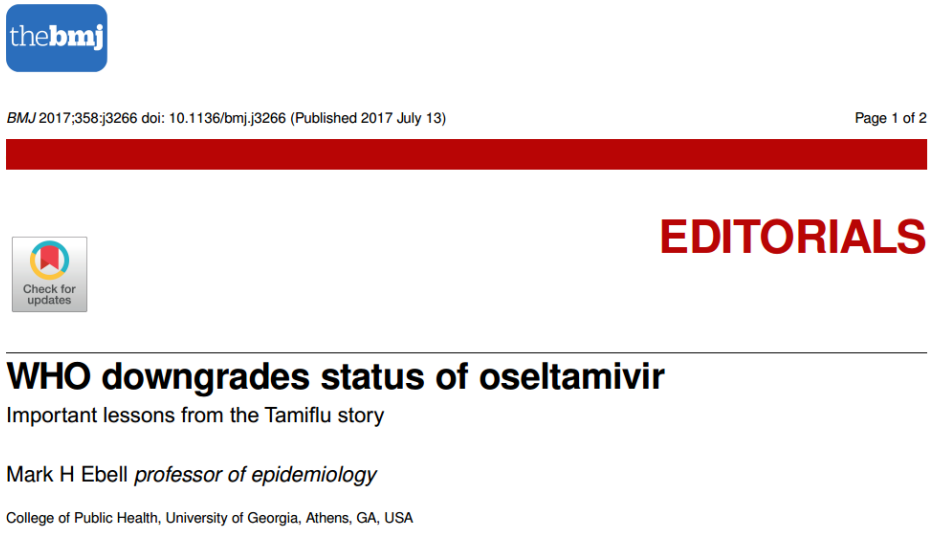
Conclusions: Oseltamivir and zanamivir cause small reductions in the time to first alleviation of influenza symptoms in adults. The use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. Oseltamivir has no protective effect on mortality among patients with 2009A/H1N1 influenza. Prophylaxis with either NI may reduce symptomatic influenza in individuals and in households. The balance between benefits and harms should be considered when making decisions about use of NIs for either prophylaxis or treatment of influenza.

2017

World Health Organization

Section 6.4.3: Other antivirals

The Expert Committee did not recommend the deletion of oseltamivir from the EML and EMLc, recognizing that it is the only medicine included on the Model Lists for critically ill patients with influenza and for influenza pandemic preparedness. However, the Committee noted that compared to when oseltamivir was first included on the Model List in 2009, there now exists additional evidence of oseltamivir in seasonal and pandemic flu which has reduced the previously estimated magnitude of effect of oseltamivir on relevant clinical outcomes. The Committee recommended the listing of oseltamivir be amended and the medicine be moved from the core to the complementary list, and its use be restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients. The Expert EML Committee noted that WHO guidelines for pharmacological management of pandemic and seasonal influenza are going to be updated in 2017: unless new information supporting the use in seasonal and pandemic outbreaks is provided, the next Expert Committee might consider oseltamivir for deletion.



thebmj

BMJ 2017;358:j3266 doi: 10.1136/bmj.j3266 (Published 2017 July 13) Page 1 of 2

Check for updates

EDITORIALS

WHO downgrades status of oseltamivir

Important lessons from the Tamiflu story

Mark H Ebell *professor of epidemiology*

College of Public Health, University of Georgia, Athens, GA, USA

The Committee recommended the listing of oseltamivir be amended and the medicine be moved from the core to the complementary list, and its use be restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.

https://www.cebm.net/2016/06/timeline-events-since-publication-cochrane-review-neuraminidase-inhibitors/

Knowledge is the enemy of disease, The application of what we know will have a bigger impact on health and disease than any single drug or technology likely to be introduced in the next decade.

In the 21st century, knowledge is the key element to improving health. In the same way that people need clean, clear water, they have a right to clean, clear knowledge.

Sir Muir Gray
Director of the UK's National Health Service (NHS) National Knowledge Service

1. Promoting transparent reporting

CONSORT

PRISMA
TRANSPARENT REPORTING

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Library for health research reporting

The Library contains a comprehensive searchable database of reporting guidelines and also links to other resources relevant to research reporting.

- Search for reporting guidelines
- Not sure which reporting guideline to use?
- Reporting guidelines under development
- Visit the library for more resources

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions	Other
Observational studies	STROBE	Extensions	Other
Systematic reviews	PRISMA	Extensions	Other
Case reports	CARE	Extensions	Other
Qualitative research	SRQR	COREQ	Other
Diagnostic / prognostic studies	STARD	TRIPOD	Other
Quality improvement studies	SQUIRE		Other
Economic evaluations	CHEERS		Other
Animal pre-clinical studies	ARRIVE		Other
Study protocols	SPIRIT	PRISMA-P	Other
Clinical practice guidelines	AGREE	RIGHT	Other

See all 374 reporting guidelines

UK EQUATOR Centre Publication School, June 2017, St Catherine's College, Oxford

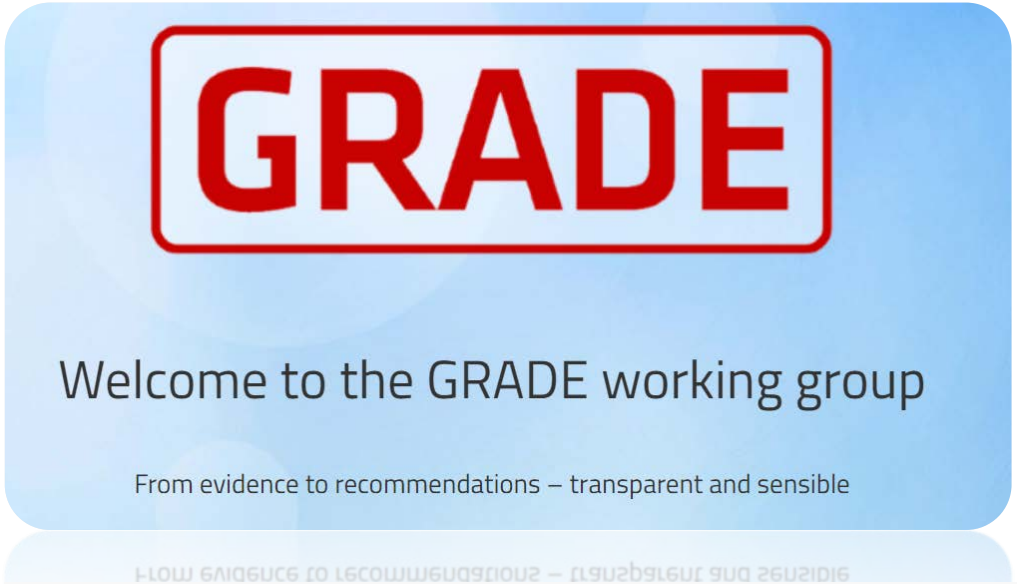
1. Promoting transparent reporting

RESEARCH AND REPORTING METHODS **Annals of Internal Medicine**

A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement

Yaolong Chen, PhD, MMed; Kehu Yang, MMed*; Ana Marušić, MD, PhD; Amir Qaseem, MD, PhD, MHA; Joerg J. Meerpohl, MD; Signe Flottorp, MD, PhD; Elie A. Akl, MD, MPH, PhD; Holger J. Schünemann, MD, PhD; Edwin S.Y. Chan, PhD; Yngve Falck-Ytter, MD; Faruque Ahmed, PhD; Sarah Barber, PhD; Chiehfeng Chen, MD, MPH, PhD; Mingming Zhang, MSc; Bin Xu, MD; Jinhui Tian, PhD; Fujian Song, PhD; Hongcai Shang, MD, PhD; Kun Tang, PhD; Qi Wang, MMed; and Susan L. Norris, MD, MPH, MSc*; for the RIGHT (Reporting Items for Practice Guidelines in Healthcare) Working Group†

2. Rating evidence and recommendations



Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	

The GRADE working group

The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations. Many international organizations have provided input into the development of the GRADE approach which is now considered the standard in guideline development.

G. Guyatt et al. / Journal of Clinical Epidemiology 64 (2011) 383–394

2. Rating evidence and recommendations

GRADE centers

McMaster University GRADE Center
Lanzhou University GRADE Center
Barcelona GRADE Center
Freiburg University GRADE Center
American University of Beirut GRADE Center
Lazio Region-ASL Rome GRADE Center
Javeriana Bogota GRADE Center
JBI Adelaide GRADE Center

GRADE networks

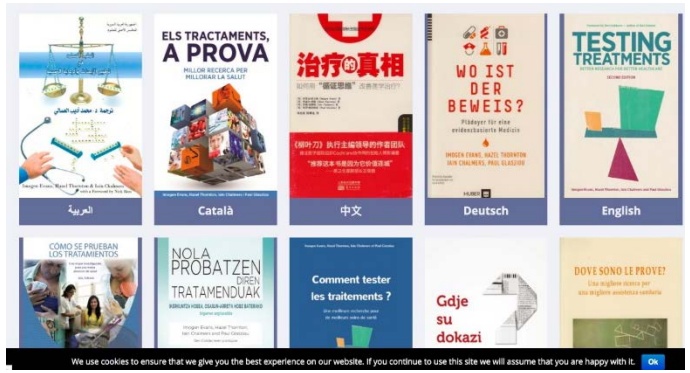
U.S. GRADE Network
Dutch GRADE Network
UK GRADE Network

Groups and projects

DECIDE research project
Environmental health
Prognosis
Outcomes valuation
GRADE-CERQual
Diagnosis
Network meta-analysis
Observational studies
GRADE training and credentialing
Public health
Rare diseases
Evidence to decision
Equity
Algorithms and pathways
Modeling
Biosimilars
Animal studies
Complex interventions
GRADE NRS risk of bias integration

3. Involving patients and public

Testing Treatments *interactive*
Promoting critical thinking about treatment claims

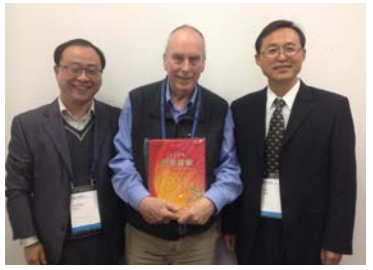


Vision

TTi seeks to promote a world in which health professionals, patients and the public use reliable research to inform their health decisions.

Missions

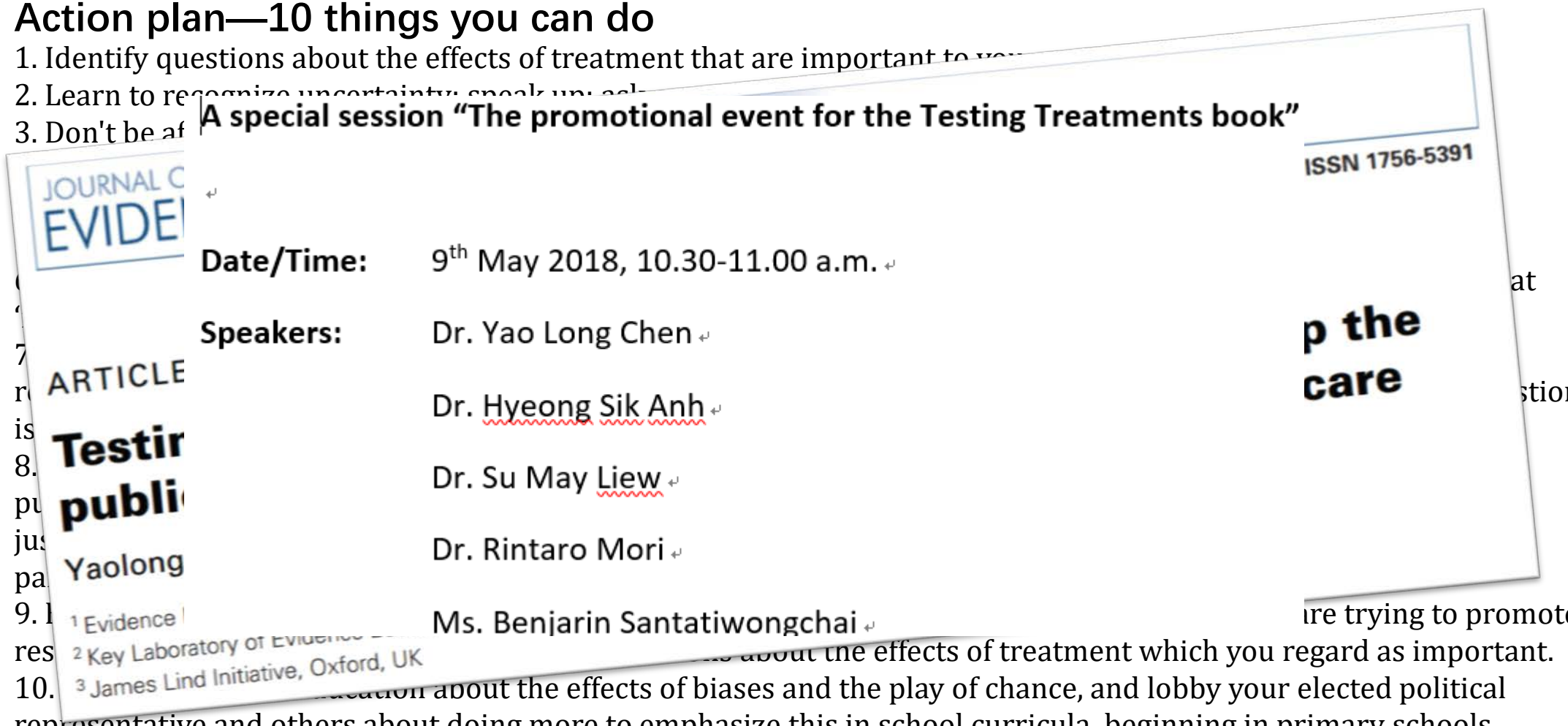
To promote a global network, involving members of the public in partnership with professionals, to communicate and discuss basic principles and general knowledge about testing treatments;
To help the public increase critical thinking and skills in accessing, apprehending, appraising and using research evidence;
To help patients and the public to participate more actively in health research.



3. Involving patients and public

Action plan—10 things you can do

1. Identify questions about the effects of treatment that are important to you
2. Learn to recognize uncertainty; speak up; ask
3. Don't be af



JOURNAL C
EVIDE

ISSN 1756-5391

ARTICLE

Testir
publi

Yaolong

[1] Evidence
[2] Key Laboratory of Evidence
[3] James Lind Initiative, Oxford, UK

A special session "The promotional event for the Testing Treatments book"

Date/Time: 9th May 2018, 10.30-11.00 a.m.

Speakers: Dr. Yao Long Chen

Dr. Hyeong Sik Anh

Dr. Su May Liew

Dr. Rintaro Mori

Ms. Benjarin Santatiwongchai

p the
care

at

stion

re trying to promote

about the effects of treatment which you regard as important.

10. ucation about the effects of biases and the play of chance, and lobby your elected political representative and others about doing more to emphasize this in school curricula, beginning in primary schools.

Thank you very much !

chenyaolong@lzu.edu.cn