Institution: University College London

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Changing international guidance on sodium-containing medications to improve cardiovascular health

Period when the underpinning research was undertaken: 2011 - 2013

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Li Wei	Professor; Chair in Pharmacoepidemiology and Drug Safety Research	2012 - present

Period when the claimed impact occurred: 2013 - present

Is this case study continued from a case study submitted in 2014? No

Summary of the impact

Joint research by UCL and the University of Dundee was the first to determine and address the cardiovascular health significance of long-term sodium consumption from medications (specifically effervescent, dispersible and soluble formulations in which high sodium levels are present). This led to a European Medicines Agency (EMA) directive to ensure that the sodium content is clearly labelled. After publication of the directive, the mean prescription levels of these medications decreased from 1089/10,000 to 841/10,000 members of the UK population, while there was also a corresponding 4.5 fold rise in the annual rate of decrease of prescriptions for high sodium medications.

2. Underpinning research

The consumption of excess sodium, principally through dietary salt, is now well established as a significant contributory factor to conditions such as hypertension, cardiovascular disease and stroke. Current NHS guidelines recommend a maximum salt daily intake of 6g/ day (equivalent to 2.4g or 104mmol sodium) for adults; patients with diagnosed conditions such as hypertension are also routinely recommended to reduce their intake. However, research by Wei and collaborators at the University of Dundee [**R1**] highlighted that medications may also play an important role in increasing sodium intake, particularly with formulations associated with rapid dispersion in water (effervescent, dispersible and soluble) which may contain additional sodium. For example, a single dispersible tablet of paracetamol may contain 18.6mmol sodium, hence moderate repeat daily dosing may contribute significantly to the daily total. At the time the study was conducted (2013), sodium content and labelling was regulated for foods but there was no such requirement for medications. The authors hypothesised that sodium-rich formulations may contribute directly to cardiovascular disease, particularly via long term use of high sodium medications [**R2**].

Li Wei's contribution to [**R1**] included study design, securement of funding, data analysis, manuscript preparation and her role as study guarantor. The study commenced in November 2011 and she moved to UCL from Dundee in July 2012; the study was submitted for publication in June 2013, with all the intensive data analyses being conducted at UCL. The subsequent peer-reviewed paper was shortlisted for The BMJ Awards 2014 (Research Paper Shortlist). Wei led and was corresponding author for the follow up study to evaluate the impact of [**R1**] on prescribing practices.

The investigation [**R1**] used a nested case control study to compare cardiovascular events in patients prescribed sodium-containing formulations with those prescribed standard tablet or capsular forms of the same drugs. Specifically, the Antithrombotic Trialists' Collaboration

(ATC) serious vascular event composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or vascular death was utilised. The authors identified 24 high sodium-containing formulations (dispersible, effervescent, and soluble) and a further 116 comparable standard formulations (non-dispersible, non-effervescent, or non-soluble versions) of the same drugs including paracetamol, aspirin, calcium carbonate, and zinc sulphate. Data from a cohort of 1,292,337 UK Primary Care Patients registered on the Clinical Practice Research Datalink (CPRD) were studied, with the basic selection criteria being age >18 and the patient taking at least two sodium-rich formulations or matched standard formulations of the same drug between January 1987 and December 2010. The mean follow-up time was 7.23 years while the median time from date of first prescription (that is, date of entry into cohort) to the first event was 3.92 years.

A total of 61,072 patients with an incident cardiovascular event were matched with controls. The study reported a 16% increase in a composite primary endpoint of incident non-fatal myocardial infarction, non-fatal stroke or vascular death, a seven-fold (odds ratio 7.18 (95% confidence interval 6.74 to 7.65) increase in the risk of developing hypertension, a 22% increase in risk of incident stroke and a 28% increase in all-cause mortality in patients who were prescribed high sodium content versions of the selected medications compared to matched patients taking the same medications in non-effervescent, soluble or dispersible forms. A test for linear trends showed there was significant trend in the dose-response relationship, indicating that risk increased with higher medication intake. The authors concluded that the use of high sodium-content formulations was associated with significantly increased chances of adverse cardiovascular events compared with standard formulations of the same drugs.

3. References to the research

[R1] George J, Majeed W, Mackenzie IS, Macdonald TM, Wei L. Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. BMJ. 2013 Nov 26;347:f6954. doi: 10.1136/bmj.f6954.

[R2] Wei L, Mackenzie IS, MacDonald TM, George J. Cardiovascular risk associated with sodium-containing medicines. *Expert Opin. Drug Saf*. 2014 Nov;13(11):1515-23. doi: 10.1517/14740338.2014.970163.

4. Details of the impact

Excess dietary sodium is a worldwide public health problem. The significant health risks posed by medications containing excess levels of sodium are well recognised as having major and dangerous consequences amongst the adult population by increasing the likelihood of stroke, heart attacks and other vascular related deaths. Research by UCL and the University of Dundee has resulted in the changing of guidelines and regulations determining the sodium content of medical products as well as raising broader awareness of the issue on health, wellbeing and prescribing practice. This is also the first time that research has been undertaken into the impact of commonly prescribed medicines which has demonstrated the detrimental long-term risks of high sodium containing medicines.

The findings of UCL and Dundee's research reported in their BMJ paper [**R1**] were used by the Director, Vigilance and Risk Management of Medicines (Medicines and Healthcare Products Regulatory Agency) to write and communicate findings on the effects of excess dietary sodium to the EMA (European Medicines Agency). This has in turn led to the publication of European-wide guidance on the relabelling of medicines. As the MHRA Director states: *"The UK presented the issue and its expert advice to several European bodies in 2014/2015 including the Pharmacovigilance Risk Assessment Committee (PRAC), the Excipients Drafting Group (ExcpDG), the European Medicines Agency's Paediatric Committee (EMA's PDCO) and the Co-ordination Group for Mutual Recognition and Decentralised*

Procedures (CMDh). A consensus view was reached and new guidance for sodium labelling was published in a PRAC recommendation in April 2015" [**S1**].

The EMA's new guidance [**S2**] has changed the way in which medicinal products are labelled and packaged in Europe. It is now compulsory for medicines with a sodium content in excess of > 1mmol (23mg) per dose to be labelled both as mg per dose and as a percentage of the recommended daily dietary intake of sodium for an adult; this is stated in the Patient Information Leaflet (PIL) and Summary of Product Characteristics (SPC). For medicines with a sodium content above 17mmol (391mg) in the maximum daily dose and a daily use for > 1 month or repeated use > 2 days every week, the sodium content must also be provided in the PIL as described above, but with the addition '*discuss with a doctor or pharmacist, especially if advised to follow a low salt (sodium) diet*' to the recommended text [**S2**]. The requirements are also retrospective for existing medications; following the publication of the EMA's guidelines, all Marketing Authorisation Holders (MAH) are required to submit Variation Documentation within 12 months of the new policy. This ensures that the labelling of all medicines manufactured, sold or consumed in Europe are updated to include warnings on the effects of sodium loading with prolonged use.

Effervescent medical supplements and painkillers have also been highlighted as a high source of sodium intake in the NHS salt guidelines as part of the broader UK government Eat Well campaign providing advice to Britons for achieving a healthy, balanced diet: "*If you routinely take an effervescent (dissolvable) vitamin supplement, or take effervescent painkillers when necessary, it's worth remembering that these can contain up to 1g salt per tablet. You may therefore wish to consider changing to a non-effervescent tablet, particularly if you have been advised to watch or reduce your salt intake*" [**S3**].

The original study has been followed up by a paper that indicates that there has subsequently been a significant decrease in the prescriptions of high sodium containing medications [**S4**]. Using data from The Health Improvement Network (THIN) database (a UK wide database that captures approximately 6% of the population), a total of 3,651,419 prescription records from 446,233 patients were analysed. A comparison was made between the prescription rates of high sodium medicines before and after the original publication, as well as the period after the EMA guidelines were published. The findings demonstrate that prescription rates of high sodium-containing medications changed from 1029.33/10,000 inhabitants (2009-2013) to 841.33/10,000 inhabitants after the publication (2014-2018) (P=0.004). In addition, the number of prescriptions decreased from 959.51 prescriptions per 10,000 inhabitants during the period of 2013-2015 to 776.60 prescriptions per 10,000 inhabitants during the period of 2016-2018 (P=0.003), after publication of the EMA guidelines. The average annual percentage change in prescriptions decreased from -1.54% to -6.88%, indicating a 4.5 fold rise in the annual rate of decrease of prescriptions for high sodium medications. This is clear evidence that the study has resulted in a significant decrease in the prescription of high sodium-content medications, with commensurate benefits to patient wellbeing.

The results of this research have generated widespread media interest and has been featured in national and international news bulletins, with the BMJ listing 32 new outlets [**S5**]. In the UK alone, this has included coverage about the dangers of high sodium levels in drugs on BBC News, Guardian, Daily Mail and Daily Telegraph [**S6**, **S7**, **S8**, **S9**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[S1] Testimonial from Director of the VRMM, MHRA
[S2] EMA recommendations and Q&A: Sodium in the context of revision of guidelines 'Excipients in the label and package leaflet of medicinal products for human use' p.3. https://www.ema.europa.eu/documents/regulatory-procedural-guideline/draft-questions-answers-sodium-context-revision-guideline-excipients-label-package-leaflet-medicinal_en.pdf; https://www.ema.europa.eu/en/documents/prac-

recommendation/prac-recommendations-signals-update-product-information-adopted-7-10-april-2015-prac_en.pdf.
[S3] https://www.nhs.uk/live-well/eat-well/salt-nutrition/
[S4] Ju C, Wei L, Mackenzie IS, MacDonald TM, George J. Changes in prescribing rates of sodium-containing medications in the UK from 2009 to 2018 BMJ Open 2021. doi:10.1136/bmjopen-2020-043566
[S5] https://www.bmj.com/content/347/bmj.f6954/article-info
[S6] https://www.bbc.co.uk/news/health-25091741
[S7] https://www.theguardian.com/science/2013/nov/27/salt-level-drugs-health-risk
[S8] https://www.dailymail.co.uk/health/article-2514144/The-painkillers-contain-salt-Soluble-versions-paracetamol-aspirin-ibuprofen-patients-22-risk-strokes.html
[S9] https://www.telegraph.co.uk/news/health/news/10475757/Warning-over-stroke-risk-from-soluble-painkillers.html