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| **Institution:** University of Dundee | | |
| **Unit of Assessment:** UoA 1 Clinical Medicine | | |
| **Title of case study:** The impact of sodium containing effervescent, soluble and dispersible drugs on cardiovascular events | | |
| **Period when the underpinning research was undertaken:** 2011-2013 | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):**<br><br>Professor Jacob George | **Role(s) (e.g. job title):**<br><br>Professor of Cardiovascular Medicine & Therapeutics | **Period(s) employed by submitting HEI:**<br>2003 to date |
| **Period when the claimed impact occurred:** 2013 to date | | |
| **Is this case study continued from a case study submitted in 2014?** N | | |

## 1. Summary of the impact

Excess dietary sodium is a major public health problem worldwide. In 2013 Professor **George** showed for the first time that long-term consumption of sodium-containing effervescent, soluble and dispersible medications caused significant increases in cardiovascular events and incident hypertension. These findings were adopted by the Pharmacovigilance and Risk Assessment Committee of the European Medicines Agency. The labelling, Summary of Product Characteristics and patient leaflets of such medications manufactured, sold or consumed in Europe must now warn consumers of the associated risk and state their sodium content. Subsequent analysis has shown prescribing of these medications to have reduced significantly since 2013.

## 2. Underpinning research

The causal link between sodium intake and cardiovascular risk is well established. By the early 2000s, considerable efforts were being made to reduce population salt intake via the diet. **George**, however, recognised that a significant sodium load can be ingested via certain medications such as effervescent, dispersible and soluble formulations. The recommended sodium intake for an adult in the UK is 2.4 g per day (104 mmol). However, dispersible and effervescent formulations of paracetamol (500 mg) can contain as much as 18.6 mmol and 16.9 mmol of sodium per tablet respectively; the maximum daily dose of eight tablets therefore results in the ingestion of 148 mmol and 135 mmol of sodium respectively **[R1]**. This, when added to a typical Western diet, could result in very high sodium intake; however, before **George**'s work there was no requirement to highlight it with a warning in labelling or prescribing advice.

Irrespective of the associated anion, sodium loading is detrimental in terms of circulating volume expansion, potentially leading to hypertension and other downstream cardiovascular events, particularly stroke and myocardial infarction. The major impact of sodium ingestion on hypertension results from increased $Na^+$ re-absorption in the renal tubules via $Na^+$-water exchange; diuresis is therefore the cornerstone of hypertension management in salt-sensitive patients. Sodium loading of healthy individuals impairs vascular endothelial function, left ventricular relaxation and cardiac repolarisation. Some of these effects may be independent of blood pressure in hypertensive patients.

In 2013, **George** and colleagues published a nested case-control study in a validated general practice database of 1.29 million UK residents **[R2]**. Cases (n = 61,072) who received at least two prescriptions of a sodium-containing effervescent, soluble or dispersible medication between January 1987 and December 2010 were compared with an equal number of well-matched

controls prescribed medications containing the same active pharmaceutical ingredients in non-effervescent/soluble/dispersible form. The mean follow-up time was 7.23 years. The median sodium consumption from sodium-containing medications alone in the study was 2.5 g/day, exceeding the current recommended sodium daily intake of 2.4 g/day **[R3]**.

The study identified a seven-fold increase in the risk of developing hypertension (odds ratio 7.18; 95% confidence interval 6.74 to 7.65), a 16% increase in a composite primary endpoint of incident non-fatal myocardial infarction, non-fatal stroke or vascular death, a 22% increase in risk of incident stroke and a 28% increase in all-cause mortality **[R2]**. The key difference between the cases and controls was their sodium intake via effervescent, soluble and dispersible medications.

A test for linear trends identified a significant trend in the dose-response relationship. When a propensity analysis was performed to account for prescription bias the propensity scores for cases and controls were very similar (0.93 vs 0.92).

This study suggested that physicians should prescribe sodium-containing formulations with caution and avoid administering them to patients at risk of hypertension. Furthermore, patients prescribed these formulations should be carefully monitored for the emergence of hypertension.

## 3. References to the research

**[R1] George,** J, Majeed, W, Mackenzie, I, Macdonald, T & Wei, L (2014), Salt in effervescent and dispersible medications: prescriber beware, *Prescriber*, vol. 25, no. 7, pp. 6-8. https://doi.org/10.1002/psb.1182.

**[R2] George,** J, Majeed, W, Mackenzie, IS, MacDonald, TM & Wei, L (2013), Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study, *BMJ*, vol. 347, f6954. https://doi.org/10.1136/bmj.f6954. This paper was shortlisted as a finalist for the 2014 BMJ UK Research Paper of The Year Award.

**[R3]** Wei, L, Mackenzie, IS, MacDonald, TM & **George**, J (2014), Cardiovascular risk associated with sodium-containing medicines, *Expert Opinion on Drug Safety*, vol. 13, no. 11, pp. 1515-1523. https://doi.org/10.1517/14740338.2014.970163.

### Funding

Tenovus Scotland (2011-2013): The effect of high-sodium content in commonly available dispersible medicines on the incidence and prevalence of hypertension, T10/12, £10,000, Jacob **George**

## 4. Details of the impact

Before 2013 the risks of long-term consumption of sodium-containing effervescent, soluble and dispersible medications had not been characterised and manufacturers were not required to highlight the sodium content of prescription or over-the-counter medications. **George**'s work **[R2]** therefore highlighted an important but overlooked source of ingested sodium. Subsequently, information campaigns, regulatory action and lobbying ensured proper labelling of sodium-containing formulations to help prescribing professionals and consumers of over-the-counter products make informed decisions when choosing which products to use.

### Changes in prescribing as a direct result of George's work

Analysis of prescribing trends using The Health Improvement Network (THIN) and Prescription Cost Analysis databases indicated that **George**'s publication **[R2]** influenced prescribing practices for sodium-containing medications in the UK **[E1]**. Interrupted time series analysis of THIN data showed that the monthly prescribing rate of sodium-containing formulations was

stable between 2009 and 2013; however, following publication of [**R2]** the slope reduced significantly by 0.26 per month (95% confidence interval -0.45 to -0.07; p=0.009). The slope for non-sodium standard formulations did not change.

**Regulatory and labelling changes**

**George**'s work triggered action on salt in effervescent medications at both UK and EU level; according to the Director of Vigilance and Risk Management of Medicines, MHRA **[E2]**:

> The paper was evaluated and discussed at several of the Agency's Commission on Human Medicines (CHM) Expert Advisory Groups (EAGs) in 2013/2014…There was agreement that the labelling of sodium in product information at the time of the paper, did not provide meaningful information to guide clinicians, pharmacists or patients and help them choose appropriate medicines in terms of sodium content.
>
> All Expert Groups advised that the high levels of sodium in some medicines, particularly those that dissolve, should be highlighted in the product information of all medicines containing different levels of total sodium.
>
> 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).

**George**'s results were also highlighted in a report presented to the UK Parliament in 2015 by the Commission on Human Medicines and the British Pharmacopoeia Commission **[E3]**.

Responding to **George**'s findings, the EMA commissioned a Europe-wide signal detection programme to assess the impact of sodium-containing medications on cardiovascular health. In 2015 the PRAC published new guidance for sodium labelling and recommended an update to the EMA Excipient Guidelines **[E4, E5]**.

In October 2017 the European Commission updated its Excipient Guideline to require all Marketing Authorisation Holders to submit Variation Documentation within 12 months. The labelling of medicines manufactured, sold or consumed in Europe now features warnings about the effects of sodium loading with prolonged use. For medications exceeding 17 mmol/tablet the Summary of Product Characteristics and Patient Information Leaflet must both state how much sodium they contain.

**Impacts on professionals – doctors, prescribers, pharmacists and dispensers**

**George**'s work and the consequent change in labelling regulations have triggered changes in prescribing advice which have been promulgated internationally via websites aimed at prescribing professionals (e.g. [**E6]**) and influenced recent updates to NICE Guidance; for example, the August 2020 update to NICE guidance on "Analgesia - mild-to-moderate pain" **[E7]** contains a scenario on paracetamol which advises:

> Avoid effervescent preparations of paracetamol where possible, particularly in people with hypertension, heart failure, and renal failure — if oral paracetamol is required in a person with swallowing difficulty, use paracetamol suspension in place of effervescent preparations (which contains up to 6 g salt in a 4 g per 24 hours dose).

[text removed for publication]

### Impacts on consumers/patients

Educating clinicians about the risks of consuming high-salt containing medications helps to protect patients receiving them by prescription; however, many over-the-counter effervescent medications also contain high salt concentrations. Package labelling and inserts must now provide consumers of over-the-counter products with the information they need in order to make an informed decision about their use (e.g. **[E9]**).

### Influence on the wider debate on dietary sodium intake

In 2014 **George** was invited to join Consensus Action on Salt and Health (CASH, now called Action on Salt **[E10]**). This group of 25 internationally recognised scientific experts has persuaded the Department of Health (England) to mandate a further 10% reduction in salt thresholds from its 2012 targets with the aim of saving 6000 lives each year.

The Director of Vigilance and Risk Management of Medicines at the MHRA confirms that **George**'s study "raised an important potential public health issue" **[E2]**. European Medicines Labelling Legislation changed as a result, thus reducing the prescribing of potentially harmful high-sodium medications, ensuring the provision of better information to consumers of over-the-counter medications and contributing to efforts to reduce dietary sodium intake worldwide.

## 5. Sources to corroborate the impact

**[E1]** Ju, C, Wei, L, Mackenzie, IS, MacDonald, TM & **George**, J (2021), Changes in prescribing rates of sodium-containing medications in the UK from 2009 to 2018: a cross-sectional study with interrupted time series analysis, *BMJ Open*, vol. 11, no. 2, e043566. https://doi.org/10.1136/bmjopen-2020-043566. The ITSA is presented in Table 1.

**[E2]** Director, Vigilance and Risk Management of Medicines, Medicines and Healthcare Products Regulatory Agency 2019. Impact of the *Association of cardiovascular events with sodium-containing effervescent, dispersible and soluble medications; Nested case-control study*, by **George** *et al*, 2013 BMJ. Letter of Support, 8th February 2019.

**[E3]** Commission on Human Medicines & British Pharmacopoeia Commission 2015. Human Medicines Regulations 2012 Advisory Bodies Annual Report 2014. London: Medicines & Healthcare Products Regulatory Agency (MHRA). Sodium-containing effervescent, dispersible and soluble medications and cardiovascular events are discussed under *Safety of Marketed Medicines* (paragraph 34, page 8) and mentioned in the last bullet point of paragraph 188 on page 31. Available at https://www.gov.uk/government/publications/human-medicines-regulations-2012-advisory-bodies-annual-report-2014 [Accessed 25 February 2021].

**[E4]** Pharmacovigilance Risk Assessment Committee (PRAC) 2015. PRAC Recommendations on signals adopted at the PRAC meeting of 7-10 April 2015. European Medicines Agency. Section 1.3 (pages 6-9) addresses sodium-containing effervescent, dispersible and soluble medicines and cardiovascular events. Available at https://www.ema.europa.eu/documents/prac-recommendation/prac-recommendations-signals-adopted-prac-meeting-7-10-april-2015_en.pdf [Accessed 25 February 2021].

**[E5]** Committee for Human Medicinal Products 2015. Questions and Answers on Sodium Used as an Excipient in Medicinal Products for Human Use. European Medicines Agency. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-sodium-used-excipient-medicinal-products-human-use_en.pdf [Accessed 25 February 2021].

**[E6]** Mak WY (2016). *Salt trap: How medicine causes more harm than good*.[Online]. Available at: https://today.mims.com/salt-trap--how-medicine-causes-more-harm-than-good [Accessed 30 December 2020]. PDF available.

**[E7]** NICE. 2020. *Analgesia - Mild-to-Moderate Pain: Scenario: Paracetamol* [Online]. National Institute for Health and Care Excellence. Available: https://cks.nice.org.uk/topics/analgesia-mild-to-moderate-pain/management/paracetamol/ [Accessed 30th December 2020]. Advice on effervescent preparations of paracetamol appears halfway down the first page of the pdf print-out.

**[E8]** [Text removed for publication]

**[E9]** Omega Pharma Ltd 2020. Solpadeine Headache Soluble Tablets: Packaging and patient information leaflet (Purchased 30th December 2020). Text addressing sodium content and issues is boxed in light blue.

**[E10]** Action on Salt. 2020. *Action on Salt Members* [Online]. Available: http://www.actiononsalt.org.uk/about/cash-members/ [Accessed 23rd December 2020].