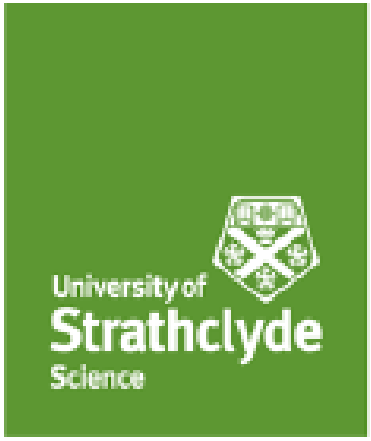
Ongoing methods across Europe to link DU and PV data to inform future prescribing

Prepared by Brian Godman



1. **Introduction**

2. ARITMO Project

3. DOACs

4. Conclusion and ways forward

Brian Godman – research activities

- PhD research activities (starting in 2006) initially in 7 EU countries to:
  - Increase the prescribing of generics first line and drive down their prices to enhance prescribing efficiency
  - Optimise reimbursement/ funding decisions for new drugs and their subsequent utilisation
- Extended across Europe and globally. Research interests including activities to improve the quality and efficiency of prescribing/ dispensing across multiple disease areas/ product classes including both infectious diseases and NCDs. This includes activities to improve ADR reporting – especially in continents such as Africa
- Co-Founder of Piperska (Europe - 2008) and MURIA (2015)
- Over 450 peer reviewed publications/ acceptances in the past 13 years (first papers from PhD published in 2008) with payers/ advisers/ academics across multiple continents/ countries. This typically includes working with health authorities and their databases – predominantly aggregated DU data – across Europe and wider (paper based in Africa and the vast majority of Asian countries I am working with)

There are considerable issues and challenges to improve medicine use across countries to improve outcomes

- Expenditure on medicines continues to grow globally at 3 – 6%/ year with growing concerns with the value of new medicines – increasingly launched early with limited data
- However – essential that medicines in high priority areas that bring substantial health benefits are funded as seen with the current COVID-19 pandemic and vaccines. However – concerns with the hype surrounding some proposed medicines, e.g. hydroxychloroquine leading to increased morbidity, mortality and costs
- Expenditure and value of medicines is a key issue across LMICs - including sub-Saharan Africa - reaching up to 60% or more of total healthcare expenditure. Much of which is out-of-pocket
- Health authority databases can be used to help enhance the appropriate use of medicines especially where there are concerns with new medicines (e.g. DOACs) and new safety data becomes available (e.g. ARITMO project, SSRIs)

We are seeing increasing use of drug utilisation and other studies to improve the managed entry of new medicines where concerns with safety/ costs. The Swedish model built on our concerns when dabigatran was first launched

FIGURE 1 | The Swedish national process for managed introduction and follow-up of new medicines. Source: The Swedish Association of Local Authorities and Regions (2017a). Reproduced with permission from Sofie Akerlind.

This was our published paper on the Swedish system – available Open Access - and builds on models we developed across Europe following the launch of DOACs

frontiers in Pharmacology

REVIEW
published: 05 October 2017
doi: 10.3389/fphar.2017.00674

The Early Awareness and Alert System in Sweden: History and Current Status

Irene Eriksson[1,2], Björn Wettermark[1,2], Marie Persson[3], Morgan Edström[4], Brian Godman[5,6,7], Anna Lindhé[8], Rickard E. Malmström[2,9], Helena Ramström[1], Mia von Euler[2,9,8] and Anna Bergkvist Christensen[10]*

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This was a study in Sweden building on this model where outcomes with Olaparib were assessed in routine clinical care using their comprehensive patient level databases. Median survival times similar to Clinical Trials and well tolerated

Targeted Oncology
https://doi.org/10.1007/s11523-018-0604-x

ORIGINAL RESEARCH ARTICLE

Real-World Use and Outcomes of Olaparib: a Population-Based Cohort Study

Irene Erlksson[1,2] · Björn Wettermark[1,2] · Kjell Bergfeldt[3]

This was the model we developed for dabigatran – endorsed by subsequent activities/ information

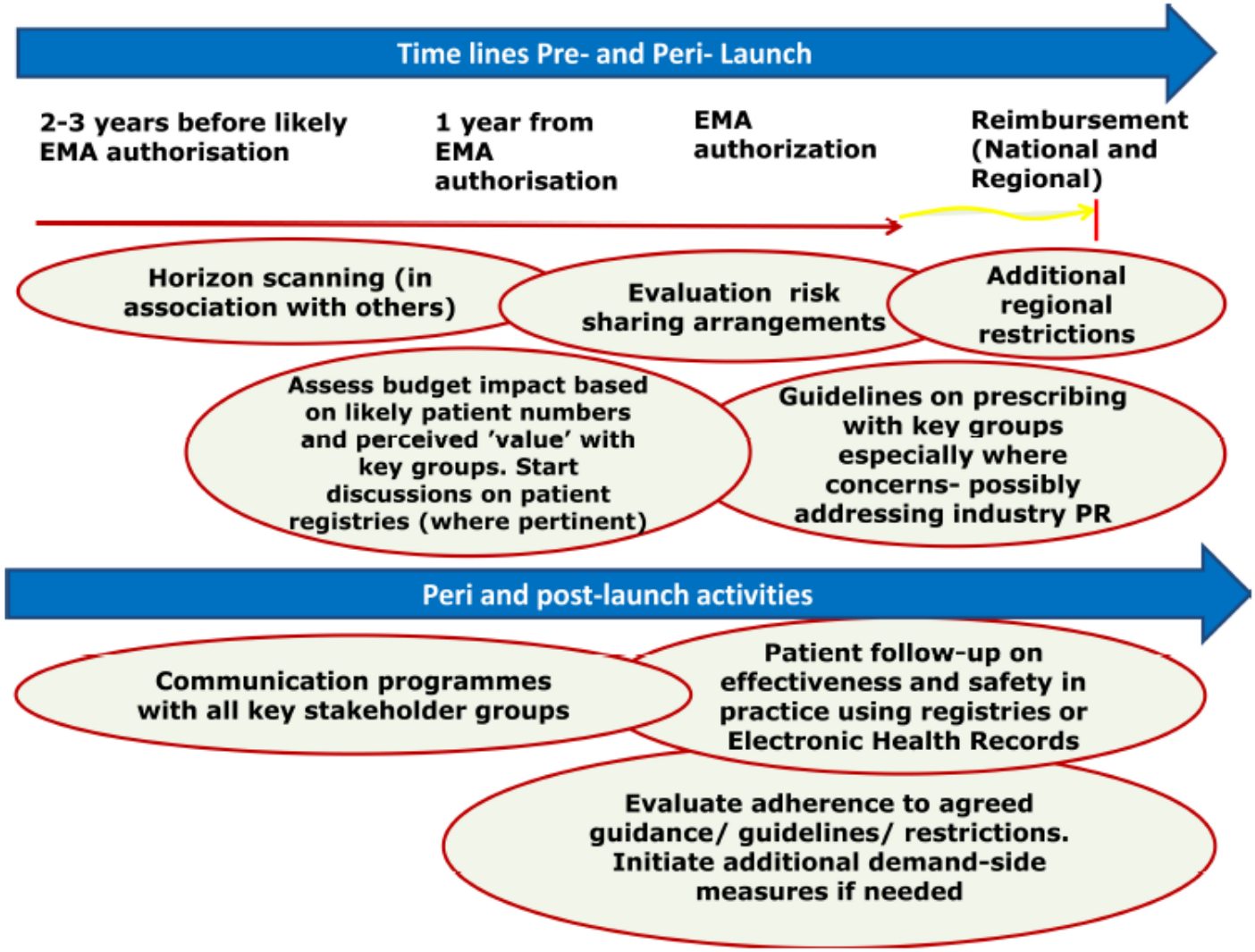

FIGURE 1 | Proposed model for optimizing the managed entry of new drugs across Europe incorporating national and regional stakeholder groups where pertinent building on the example of dabigatran.

This was our first dabigatran paper – followed up by looking at the impact of regional/ national health authority activities. No excessive bleeding/ appreciably reduced where prior educational activities until physicians became familiar with dabigatran

frontiers in PHARMACOLOGY

ORIGINAL RESEARCH ARTICLE
published: 14 May 2013
doi: 10.3389/fphar.2013.00039

Dabigatran – a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs

Rickard E. Malmström[1], Brian B. Godman[2,3,4], Eduard Diogene[5], Christoph Baumgärtel[6], Marion Bennie[4,7], Iain Bishop[7], Anna Brzezinska[8], Anna Bucsics[9], Stephen Campbell[10], Alessandra Ferrario[11], Alexander E. Finlayson[12], Jurij Fürst[13], Kristina Garuoliene[14], Miguel Gomes[15], Iñaki Gutiérrez-Ibarluzea[16], Alan Haycox[3], Krystyna Hviding[17], Harald Herholz[18], Mikael Hoffmann[19], Saira Jan[20], Jan Jones[21], Roberta Joppi[22], Marija Kalaba[23], Christina Kvalheim[17], Ott Laius[24], Irene Langner[25], Julie Lonsdale[26], Sven-Åke Lööv[27], Kamila Malinowska[28,29], Laura McCullagh[30], Ken Paterson[31], Vanda Markovic-Pekovic[32,33], Andrew Martin[34]†, Jutta Piessnegger[9], Gisbert Selke[24], Catherine Sermet[35], Steven Simoens[36], Cankat Tulunay[37], Dominik Tomek[38,39], Luka Vončina[40], Vera Vlahovic-Palcevski[41], Janet Wale[42], Michael Wilcock[43], Magdalena Wladysiuk[28], Menno van Woerkom[44], Corrine Zara[45] and Lars L. Gustafsson[2]*

1. Introduction

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There were increasing concerns with QT prolongation across Europe – requiring guidance

- There have been concerns with QT prolongation and subsequent arrhythmia-related events (i.e. Torsade de Pointes, TdP). These included the anti-psychotics and anti-histamines. There have also been concerns with certain SSRIs
- In the case of anti-psychotics – utilisation was tracked particularly for anti-psychotics of concern, i.e. one or more of ≥4 cases of TdP/QT abnormalities; significant Reporting Odds Ratio (ROR) for TdP/QT abnormalities, adjusted and stratified; ≥4 cases of ventricular arrhythmia/sudden cardiac death (VA/SCD); significant ROR for VA/SCD and significant ROR, combined by aggregating TdP/QT abnormalities with VA and SCD based on FAERS database
- There was typically a growth in anti-psychotic use across studied European countries. There was a considerable increment of Group A agents (strong torsadogenic risk) in a number of European countries providing guidance to the authorities on potential activities
- There have been similar concerns with the anti-histamines

There was typically increased prescribing of anti-psychotics across Europe

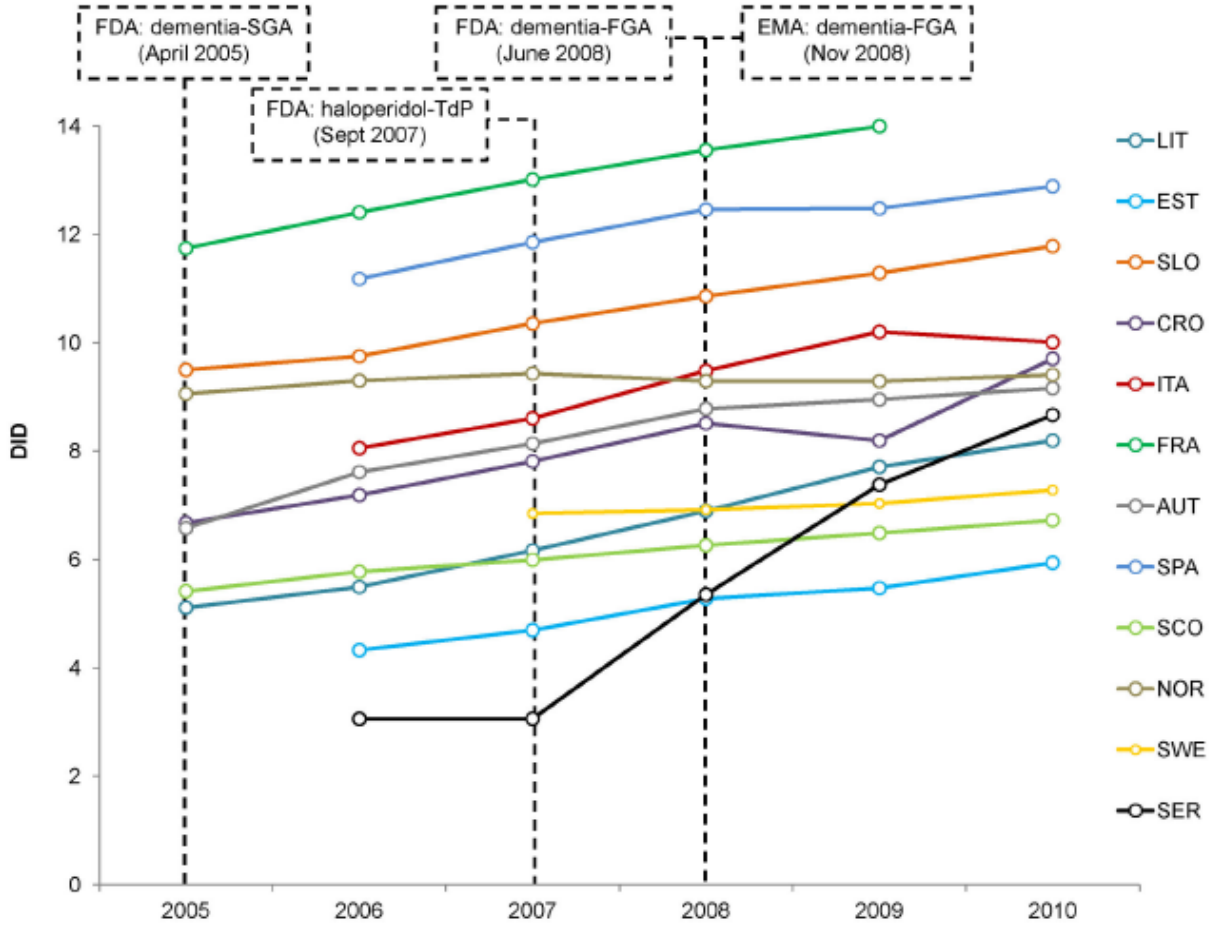

Figure 1. Trends in antipsychotic utilization according to data availability. AUT: Austria; CRO: Croatia; EST: Estonia; FRA: France; ITA: Italy; LIT: Lithuania; NOR: Norway; SPA: Spain (Catalonia); SCO: Scotland; SER: Serbia; SLO: Slovenia; SWE: Sweden; EMA: European Medicines Agency; FDA: Food and Drug Administration; FGA: first-generation antipsychotics; SGA: second-generation antipsychotics; TdP: Torsades de Pointes. Boxes indicate regulatory safety warnings on cardiovascular risk.

doi: 10.1371/journal.pone.0081208.g001

There was our published paper in PLOS in 2013

OPEN ACCESS Freely available online

PLOS | ONE

Torsadogenic Risk of Antipsychotics: Combining Adverse Event Reports with Drug Utilization Data across Europe

Emanuel Raschi[1], Elisabetta Poluzzi[1], Brian Godman[2,3], Ariola Koci[1], Ugo Moretti[4], Marija Kalaba[5], Marion Bennie[3,6], Corrado Barbui[7], Bjorn Wettermark[2,8], Miriam Sturkenboom[9], Fabrizio De Ponti[1*]

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There was again variable use of antihistamines with different torsadogenic risks across Europe

- Using the same database antihistamines were reported in 109 cases of TdP/QT prolongation, 278 VA and 610 SCD/CA (sudden cardiac death/cardiac arrest)
- Five antihistamines had stronger signals (cetirizine, desloratadine, diphenhydramine, fexofenadine, loratadine) and 6 weaker signals (alimemazine, carbinoxamine, cyclizine, cyproeptadine, dexchlorpheniramine and doxylamine)
- Exposure to antihistamines with stronger signals was markedly different among European countries and was at least 40% in each country – although limited growth overall in anti-histamine use among studied European countries
- Overall, some second-generation antihistamines are associated with signal of torsadogenicity and largely used in most European countries
- Whilst confirmation by analytical studies is required, we proposed in our paper that regulators and clinicians should consider risk-minimisation activities
- In addition, antihistamines without signals but with abnormal use in a few countries (e.g., levocetirizine) or with increasing consumption (e.g., rupatadine) deserve careful surveillance going forward

Overall stable use of antihistamines across Europe in the studied period

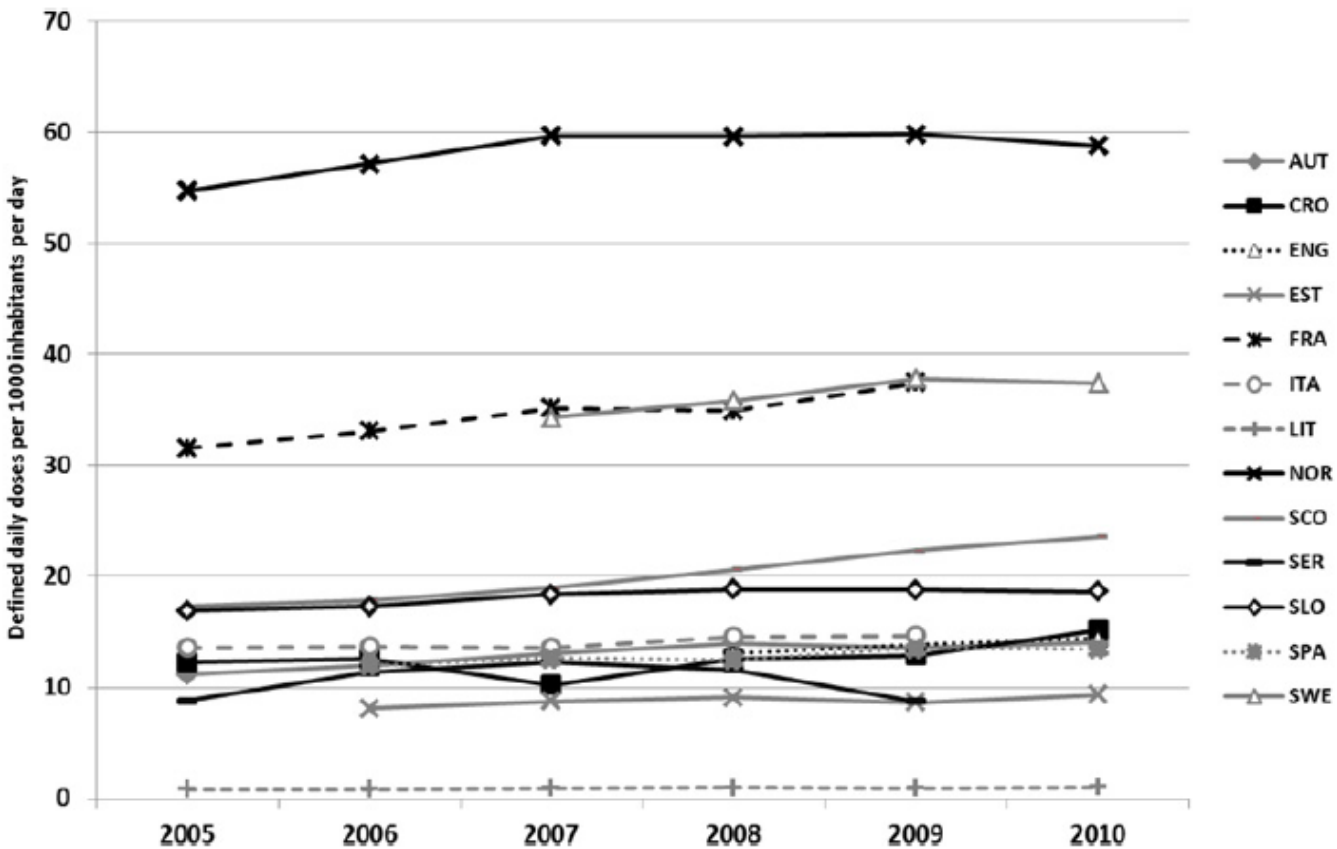

Fig 1. Cross-National Comparison: time trend. AUT: Austria; CRO: Croatia; EST: Estonia; FRA: France; IT: Italy; LIT: Lithuania; NOR: Norway; SPA: Spain (Catalonia); SCO: Scotland; SER: Serbia; SLO: Slovenia; SWE: Sweden. ENG: 2008–2010; EST: 2006–2010; FRA: 2005–2008; ITA: 2006–2010; SPA: 2006–2010; SWE: 2007–2010. Data from Norway and Sweden include also hospital data. Data from Sweden also includes OTC data.

This was our publication in 2015

PLOS | ONE

RESEARCH ARTICLE

Pro-Arrhythmic Potential of Oral Antihistamines (H1): Combining Adverse Event Reports with Drug Utilization Data across Europe

Elisabetta Poluzzi[1], Emanuel Raschi[1], Brian Godman[2,3], Ariola Koci[1], Ugo Moretti[4], Marija Kalaba[5], Bjorn Wettermark[2,6,7], Miriam Sturkenboom[8], Fabrizio De Ponti[1]*

1 Department of Medical and Surgical Sciences, Alma Mater Studiorum—University of Bologna, Bologna, Italy, **2** Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden, **3** Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, United Kingdom, **4** Clinical Pharmacology Unit, University of Verona, Verona, Italy, **5** Republic Fund for Health Insurance, Belgrade, Serbia, **6** Centre for Pharmacoepidemiology, Karolinska University Hospital, Solna, Stockholm, Sweden, **7** Stockholm, County Council, Stockholm, Sweden, **8** Erasmus University Medical Centre, Rotterdam, Netherlands

National and regional advice in Scotland regarding QT prolongation with citalopram and escitalopram coupled with monitoring of prescribing behaviour resulted in an appreciable change in habits

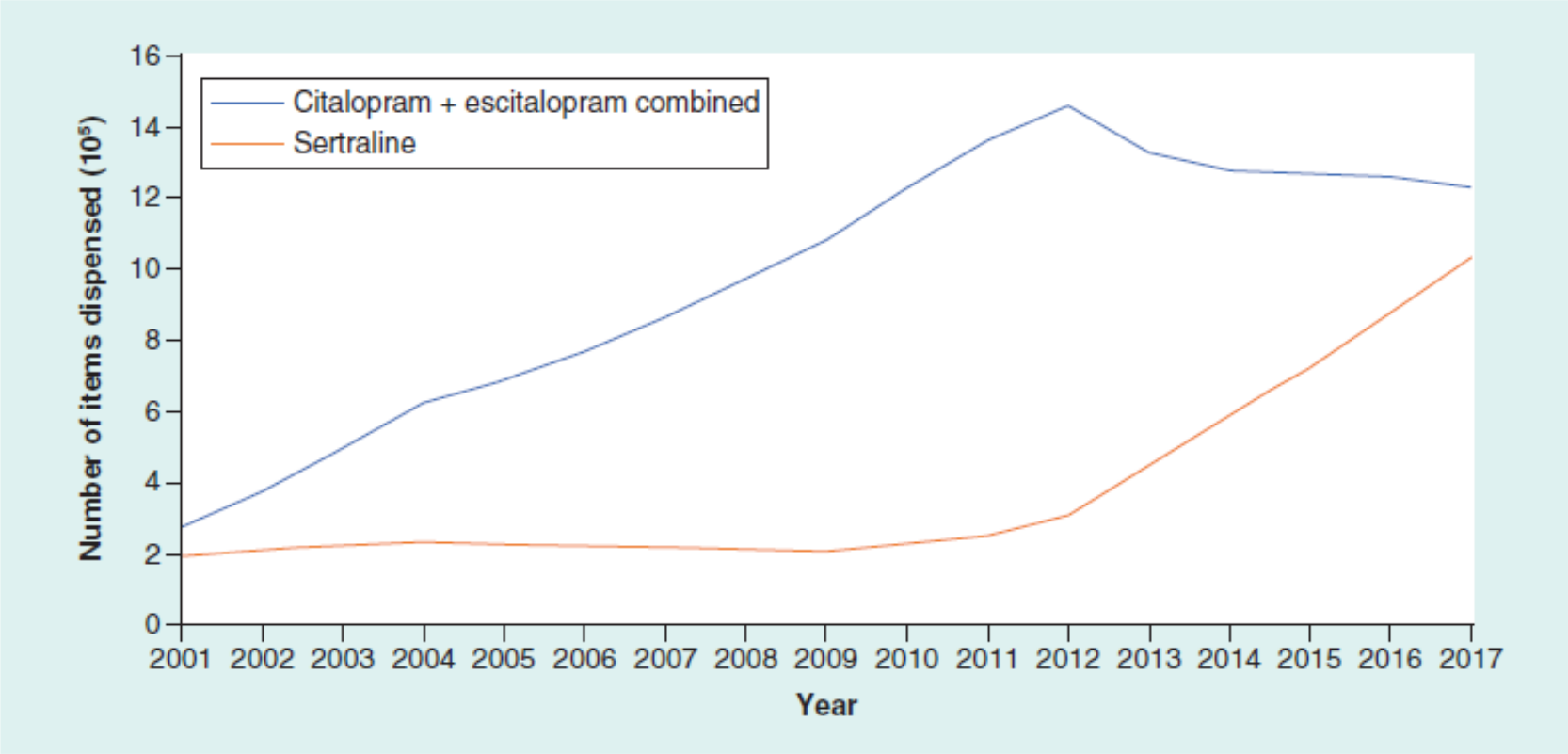

Figure 4. Extent of utilization of citalopram, escitalopram and sertraline in Scotland 2001–2017.

This was the paper we published in 2019

Research Article

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Journal of Comparative Effectiveness Research

Ongoing initiatives within the Scottish National Health Service to affect the prescribing of selective serotonin reuptake inhibitors and their influence

Brian Godman*[,1,2,3], Amanj Kurdi[1,4], Holly McCabe[5], Chris F Johnson[6], Corrado Barbui[7], Sean MacBride-Stewart[6], Simon Hurding[8], Axel Leporowski[5], Marion Bennie[1] & Alec Morton[5]

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[4]Department of Pharmacology, College of Pharmacy, Hawler Medical University, Erbil, Iraq
[5]Department of Management Science, Strathclyde Business School, University of Strathclyde, Glasgow, UK
[6]Prescribing Support Unit, National Health Service Greater Glasgow & Clyde (NHS GGC), Glasgow, UK
[7]WHO Collaborating Centre for Research & Training in Mental Health & Service Evaluation, Department of Neuroscience, Biomedicine & Movement Sciences, Section of Psychiatry, University of Verona, Italy
[8]Therapeutics Branch, Scottish Government, Edinburgh, UK
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DU studies have helped physicians and authorities gain good understanding of DOACs

- There were concerns with excessive bleeding in elderly patients prescribed DOACs leading to extensive educational activities by health authorities and others across Europe
- Follow-up studies suggested that such activities reduced excessive bleeding in practice with Maura et al using French health authority databases suggesting comparable bleeding/ ischemic risks with VKAs
- More recent follow-up in Scotland using their health authority databases suggests all DOACs are similarly effective in preventing strokes and systemic embolisms, while patients being treated with rivaroxaban exhibited the highest bleeding risks including GI bleeds and MIs higher with apixaban
- Recent Pan-European studies using patient-level data have shown that in routine clinical care both first year persistence and adherence are lower with dabigatran (persistence: 77%, adherence: 65%) compared with apixaban (86% and 75%) and rivaroxaban (83% and 75%) - giving additional guidance to health authorities and prescribers

This was the paper evaluating DOACs in France published in 2015 showing behavior similar bleeding and ischemic risks between rivaroxaban and VKAs

Stroke

OPEN

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

Géric Maura, PharmD*; Pierre-Olivier Blotière, MSc*; Kim Bouillon MD, PhD; Cécile Billionnet, MSc, PhD; Philippe Ricordeau, MD; François Alla, MD, PhD; Mahmoud Zureik, MD, PhD

This was the paper published in 2018 with colleagues in Scotland assessing effectiveness and safety of DOACs in routine clinical care with their comprehensive databases

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 422–431 422

ORIGINAL ARTICLE

Comparative safety and effectiveness of direct oral anticoagulants in patients with atrial fibrillation in clinical practice in Scotland

Correspondence Tanja Mueller, The Farr Institute of Health Informatics Research, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK. Tel.: +44 (0)141 548 2367; E-mail: tanja.muller@strath.ac.uk

Received 27 April 2018; Revised 6 November 2018; Accepted 8 November 2018

Tanja Mueller[1], Samantha Alvarez-Madrazo[1], Chris Robertson[2,3], Olivia Wu[4] and Marion Bennie[1,5]

This was the Pan-European paper assessing persistence and adherence to the different DOACs in routine care using patient level databases

ESC
European Society of Cardiology
Europace (2021) **00**, 1–9
doi:10.1093/europace/euab091

CLINICAL RESEARCH

Persistence and adherence to non-vitamin K antagonist oral anticoagulant treatment in patients with atrial fibrillation across five Western European countries

Joris J. Komen [1,2]*, Anton Pottegård[3], Aukje K. Mantel-Teeuwisse[1], Tomas Forslund [2,4], Paul Hjemdahl [4], Björn Wettermark[5], Maja Hellfritzsch[3,6], Jesper Hallas [3], Morten Olesen[3], Marion Bennie[7,8], Tanja Mueller[7], Annemarie Voss[9], Tania Schink[9], Ulrike Haug[9,10], Bianca Kollhorst[11], Øystein Karlstad[12], Lars J. Kjerpeseth[12], and Olaf H. Klungel[1,3]*

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We will see the growth in drug utilization combined with PV data bases across countries

- We will see increasing use of drug utilisation data linking with PV data to assess the safety of medicines in routine clinical care
- This is because we are seeing new medicines especially for cancer and orphan diseases launched early with often Phase II and preliminary Phase III data – and concerns whether this will reflect real life where patients can be more elderly and with greater co-morbidities. In addition – whether presumed patient benefits will be seen in practice
- We will also see greater co-operation among European countries to help with this as seen with the papers on DOACS. My colleagues and myself are currently looking at this – building on for instance the CMOP programme in Scotland
- Improvements in technologies will further assist with linking DU and PV data including greater record linkage within countries – however need reliable DU data (can be various sources as seen with antibiotic use across Europe and former Soviet Union Republics)

The CMOP programme in Scotland was initiated to improve knowledge about utilization patterns, safety and effectiveness of cancer medicines – started with prostrate cancer

Received: 16 August 2019 | Revised: 31 January 2020 | Accepted: 18 March 2020

DOI: 10.1002/pds.4998

ORIGINAL REPORT

WILEY

Use of record linkage to evaluate treatment outcomes and trial eligibility in a real-world metastatic prostate cancer population in Scotland

Kelly Baillie[1] | Tanja Mueller[2] | Jiafeng Pan[3] | Jennifer Laskey[1] | Marion Bennie[2,4] | Christine Crearie[1] | Kimberley Kavanagh[3] | Samantha Alvarez-Madrazo[2] | David Morrison[5] | Julie Clarke[1] | Aileen Keel[6] | David Cameron[7] | Olivia Wu[5] | Amanj Kurdi[2] | Robert J. Jones[1,8]

This part of ongoing programmes across Scotland to improve drug utilization – incorporating key issues including the safety of medicine use (along with value) using both aggregated and record linkage data across multiple disease areas (similar to Sweden)

Int J Clin Exp Med 2021;14(11):XXX-XXX
www.ijcem.com /ISSN:1940-5901/IJCEM0139266

Review Article

Initiatives and reforms across Scotland in recent years to improve prescribing; findings and global implications of drug prescriptions

Sean MacBride-Stewart[1], Stuart McTaggart[2], Amanj Kurdi[3,4,5], Jacqueline Sneddon[6], Stephen McBurney[7], Renata Cristina Rezende Macedo do Nascimento[8,9], Tanja Mueller[3], Hye-Young Kwon[10], Alec Morton[11], Ronald Andrew Seaton[6,12,13], Angela Timoney[3,14], Marion Bennie[3,15], Israel Abebrese Sefah[16], Alice Pisana[17], Johanna Catherine Meyer[4], Brian Godman[3,4,18]

This was our recent paper looing at the various methods to collect antimicrobial utilization data across Europe and their robustness

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 17 June 2021
doi: 10.3389/fphar.2021.639207

Variations in the Consumption of Antimicrobial Medicines in the European Region, 2014–2018: Findings and Implications from ESAC-Net and WHO Europe

Jane Robertson[1,2], Vera Vlahović-Palčevski[3], Kotoji Iwamoto[1], Liselotte Diaz Högberg[4], Brian Godman[5,6], Dominique L. Monnet[4], Sarah Garner[1], Klaus Weist[4]*
ESAC-Net Study Group and WHO Europe AMC Network Study Group

Thank You

Any Questions!

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