UNIVERSITÀ DEGLI STUDI DI PARMA

Research Doctorates in
Drugs, Biomolecules and Health Products
Cycle XXIX

Evidence Based Methodology for

Evaluation of Clinical Efficacy and Safety of Drug Therapy

A Case for Digestive Diseases

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Preface

This thesis is a "sandwich thesis" consisting of 3 individual manuscripts. At the time of writing (November -December 2016), one manuscript was partially presented as abstract at the Digestive Disease Week[1] (Chicago May 3-6, 2014) and it has been submitted in a peer reviewed journal[2], which ask some changes before accept it for publication. Two further manuscripts (Chapters 5[3] and chapter 6[4]) have been published in peer reviewed journals.

Dr. Luigi Gatta's contribution to the above works include: developing the research questions, developing the research strategies, designing the studies, writing the protocol, performing data extraction, conducting the analyses, writing up manuscripts, and responding to reviewers' comments.

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[1] Gatta L, Scarpignato C. Eradication of Small Intestine Bacterial Overgrowth With Rifaximin: A Dose- and Time-Dependent Effect. Gastroenterology 2014; 146: S465.

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[3] Scarpignato C, Gatta L, Zullo A, Blandizzi C, on behalf of the Italian Society of Pharmacology (SIF), the Italian Association of Hospital Gastroenterologist (AIGO), and the Italian Federation of General Practitioners (FIMMG). Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med 2016; 14: 179.

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Abstract

Decisions in health-care have become extremely complex and difficult since they involve a complex web of input and uncertainties. It is necessary to draw information from many sources such as primary data, preference of patients, clinical experiences, personal opinions, medical and legal regulations and, last but not least, scientific evidence. Nevertheless, the *weight* of the scientific evidence is critical, and indeed the evidence-based approach is now a "*must*". However, the number of scientific publications exploded over the last 50 years, making scientific updating very difficult. Scientific publications taken individually or in small groups selected randomly, can often present confusing and, in some cases, even contradictory results. To establish efficacy, safety as well as utility of a health-intervention it has become increasingly common performing **systematic reviews** and **meta-analyses**. These tools allow to get an updated and a comprehensive assessment (even if not the definite one) of the health-intervention evaluated. In this dissertation, we present the results of an evidence-based approach concerning three gastroenterological issues. It was assessed the effectiveness and the safety of rifaximin to treat the small intestine bacterial overgrowth (SIBO), which is a heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel, and well-recognized as cause of maldigestion and malabsorption. Rifaximin is a poorly absorbed antibiotic with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganism, both aerobes and anaerobes, fulfilling the characteristics set by DuPont and Ericsson for the ideal antimicrobial that should be used for the treatment of gastrointestinal infections. As a consequence, over the past decades, rifaximin has been largely used to treat SIBO even if there was a lack of a critical summary of evidence. Systematic reviews and meta-analyses represent the basis do draw evidence-based guidelines on drug use in given clinical conditions. By reviewing and distilling a large body of literature, we developed a Position Paper addressing benefits and harms proton pump inhibitor (PPI) therapy in the treatment of acid-related diseases. Studies in primary care and emergency settings have indeed suggested that PPIs are frequently prescribed for inappropriate indications or for indications where their use offers little benefit. Inappropriate PPI use is a matter of great concern, especially in the elderly, who are often affected by multiple comorbidities and are taking multiple medications, and are thus at an increased risk of long-term PPI-related adverse outcomes as well as drug-to-drug interactions. Finally, since National Health Systems are currently collapsing, **pharmacoeconomic analysis** represents an integral part of the decision process. However, the evaluation of economic impact of a given treatment is often biased and influenced by Companies' pressure. In this connection, we

showed that the conclusions of an article concerning tapentadol ER - in comparison with oxycodone/naloxone CR - were misleading. Indeed, with a robust methodological and meta-analytic approach we were able to show that the comparisons made by the Authors were incorrect and actually reached an opposed conclusion.

Acknowledgments

This extraordinary experience would have not been possible without my supervisor and *mentor* Professor Carmelo Scarpignato. I would like to express the deepest appreciation to him, for his constant support and for the amazing opportunities he offered to me.

I would like also to thank Professor Dino Vaira (Full Professor of Internal Medicine, University of Bologna) who introduced me, since I was a medical student, in the challenging world of research.

Finally, I would like to express my deepest gratefulness to my beloved Roberta: no words can express my gratitude for her continuous support, comprehension and patience.

List of Abbreviations

ACG: American College of Gastroenterology

AIDS: acquired immunodeficiency syndrome

AIN: acute interstitial nephritis

AP: acute pancreatitis

AIGO: Italian Association of Hospital Gastroenterologists

ARS: anti-reflux surgery

CIB: clinically important bleeding

COX: cyclooxygenase

CYP 450: cytochrome P450

CP: chronic pancreatitis

CV: cardiovascular

DDIs: drug-to-drug interactions

EBM: evidence based medicine

EoE: eosinophilic esophagitis

EPS: epigastric pain syndrome

ERT: enzyme replacement therapy

FD: functional dyspepsia

FIMMG: Italian Federation of General Practitioners

GER: gastroesophageal reflux

GERD: gastroesophageal reflux disease

GHBT: glucose hydrogen breath test

GI: gastrointestinal

H. pylori: *Helicobacter pylori*

H_2RA: H_2 receptor antagonist

IBD: inflammatory bowel disease

IBS: irritable bowel syndrome

ICU: intensive care unit

LHBT: lactulose hydrogen breath test

NAB: nocturnal acid breakthrough

NERD: non-erosive reflux disease

NNT: number needed to treat

NSAIDs: non-steroidal anti-inflammatory drugs

OTC: over-the-counter

OR: odds ratio

PDS: Postprandial distress syndrome

PPIs: proton pump inhibitors

PPI-REE: proton pump inhibitor-responsive esophageal eosinophilia

PU: peptic ulcer

RCT: randomized controlled trial

SIF: Italian Society of Pharmacology

SSRIs: selective serotonin reuptake inhibitors

SIBO: small intestinal bacterial overgrowth

SUP: stress ulcer prophylaxis

UGIB: upper GI bleeding

ZES: Zollinger–Ellison syndrome

1 Evidence Base Medicine

In 1991 an international group wanted to encourage clinicians to consider results from the most updated research to treat patients. For this reason, they started to write a series of User's Guide to reading research for JAMA, and they were looking for a new term to emphasize the intention of the series. After several suggestions, in 1992 the group's leader Gordon Guyatt proposed the term Evidence Based Medicine (EBM) [1-3]. Interest in EBM has grown fast from 1 citation in Medline in 1992[3] to over 60.000 in January 2014. Several of the most important medical journals advised to follow EBM rules of evidence[4-6], and the *New York Time* judged EBM to be the idea of the year in 2001 [7]. Moreover, the evidence based practice became to be incorporated in several disciplines including occupational therapy, physiotherapy as well as social science and even in chaplaincy [8].

During the history of medicine, three overlapping methods for determine whether treatments were effective have competed for dominance. The first considered that the effects of medical treatments had to be evaluated directly by comparing groups of people who received or not treatment [9-11]. The second believed that the underlying mechanisms of health and diseases had to be specified before concluding that a therapy caused a cure [9-12]. The third was based on authoritative pronouncements of clinical experts sometimes outplaying external evidence [13]. However, EBM has developed on the basis of the first school [13].

1.1 Definition of EBM

The current definition of EBM if the following:

"*EBM requires the integration of the best research evidence with our clinical expertise and our patient's unique values and circumstance*"[14].

By best research evidence is meant "*clinically relevant research, sometimes from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic test (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive strategies*"[14].

By clinical expertise is meant "*The ability to use clinical skills and past experience to rapidly identify each patient's unique health state and diagnosis, their individual risks and benefit of potential interventions, and their personal values and expectations*" [14].

By patient values is meant "*the unique preferences, concerns and expectations each patient brings to a clinical encounter and which must be integrated into clinical decisions if they are to serve patient*" [14].

By patient circumstances is meant "*their individual clinical state and the clinical setting*" [14].

1.2 The philosophy of EBM

The philosophy of EBM is clearly expressed in the EBM hierarchy (**Figure 1.2.1**) [15-17].

Figure 1.2.1 EBM hierarchy.

The EBM hierarchy is mainly based on 3 points: 1) systematic review and/or meta-analysis of randomized controlled trials (RCTs) or RCTs usually provide stronger evidential support than observational studies; 2) comparative clinical studies (including RCTs and observational studies) usually provide stronger evidential support than "mechanistic" reasoning ("pathophysiologic rationale") from more basic sciences; 3) comparative clinical studies in general (including RCTs and observational studies) provide stronger evidential support than expert clinical judgment [13].

1.3 The practice of EBM

The practice of EBM is based on four steps, the so-called 4A's: 1) asking clinical questions; 2) acquire the best evidences; 3) appraise the evidences; 4) apply the evidences (**Figure 1.3.1**)[14].

Figure 1.3.1 Practicing the EBM: the 4 A's.

1.3.1 Asking clinical questions

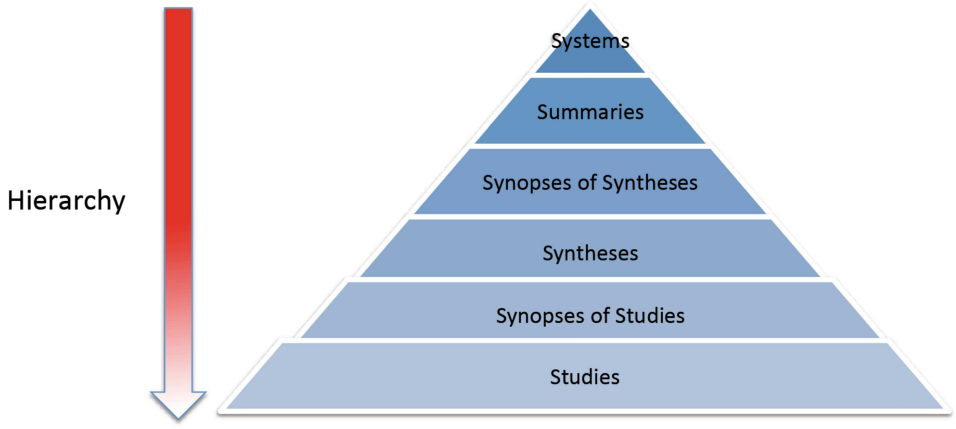
There are mainly two types of questions: the background questions commonly asked for general knowledge about a condition, test, or treatment; and the foreground questions, asked for a specific knowledge to inform clinical decisions or actions. When the experience with the condition is limited, the majority of questions could be about background knowledge. As the clinical experience growth, there will be increasing proportions of questions about the foreground managing of the patient [14].

Foreground questions have usually four essential components that can be summarize with the acronyms "PICO". **P** stands for patients, population, predicament or problem of interest; **I** stands for intervention that, using a very broadly definition, include an exposure, a diagnostic test, a prognostic factor, a treatment a patients perception, and so forth; **C** stands for comparison intervention, exposure, test, etc.; **O** stands for outcome(s) of interest including a time horizon, if relevant [14].

1.3.2 Acquire the best evidence

If we want to use high-quality evidence to make clinical decision, we need to know how to access evidence. It is a difficult task performing an exhaustive literature search and separate lower from higher quality studies. However, during the last decades, several resources have been created to facilitate the access to high-quality research. These resources are defined pre-appraised because they have undergone a filtering process to include only studies of higher quality, and they are regularly updated so that the evidence we access through these resources is current [14]. To simplify the use of these pre-appraised resources, Haynes proposed a so-called "4S" model [18] composed of four layers that, in descending hierarchy order, are: *Systems*, *Synopses*, *Syntheses*, and *Studies.* This was successively refined into a "5S" model, adding a new layer, namely *Summaries*, which preceded S*ynopses* [19]. However, in this model Synopses of systematic reviews and Synopses of studies were considered equivalent even if in the hierarchy of evidence systematic reviews are superior to single studies. For this reason, in 2009, the layer Synopses was spitted into two other layers: Synopses of Syntheses and Synopses of Studies, by becoming the "6s" model (**Figure 1.3.2**). Let's explore more in detail this model.

Figure 1.3.2 The "6S" Hierarchy of Organization of Pre-Appraised Evidence.



First of all, if we use this model to make clinical decisions, we have to begin our research at the highest possible layer, i.e. from the top of pyramid. For system is meant an evidence-based clinical information system that integrates and concisely summarizes all relevant and important research evidence about a clinical problem, that is updated as new research evidence becomes available, and that automatically links (through an electronic medical record) a specific patient's circumstances to the relevant information [20]. However, few such systems are currently available, and in this case the next best step is to look for summaries. These include clinical pathways that integrate evidence-based information about specific clinical problems and provide regular updating. Clinical Evidence (www.clinicalevidence.com), Dynamed (www.ebscohost.com/dynamed/default.php), the Physicians' Information and Education Resource (PIER) (pier.acponline.org) are some of the resources available that use explicit review processes to find and appraise evidence about the management of a wide range of clinical problems [20].

If summaries are not available, then synopses of syntheses are the next best source. A synthesis or systematic review is a comprehensive summary of all the research evidence related to a focused clinical question [20]. It involves a multistep process in which question(s) is(are) formulated, the relevant studies identified and appraised for quality, relevant study findings are extracted and synthesized either quantitatively (in the form of meta-analysis) or non-quantitatively, and conclusions are drawn. Given that often clinicians do not have the time to review detailed systematic reviews, a synopsis that summarizes the findings of a high-quality systematic review can often provide sufficient information to support clinical action[20]. ACP Journal Club (https://acpjc.acponline.org), Evidence Based Medicine (http://ebm.bmj.com), the Database of Abstracts of Reviews of Effects (DARE; http://www.crd.york.ac.uk/crdweb/) are example of resources providing *synopses.*

If more detail is needed or no synopsis is available, then syntheses (i.e. databases of systematic review) have to be checked [14]. They are based on thorough searches for evidence to provide data on effects of healthcare interventions, as the accumulated evidence will allow [14]. The Cochrane Collaboration provides the largest single source of synopses, about 30-40% of the world's supply [14].

If the above-mentioned resources are not available or they were not able to answer to a problem, then synopses of studies are the next level to check. They provide structured abstracts of individual, high quality studies, that is, studies that not only meet basic critical appraisal criteria, but also are selected for clinical relevance and interest [14]. Finally, if there are no synopses of studies, *single studies* are the last level to check [20].

1.3.3 Appraise the evidence

This is the process of carefully and systematically examining researches to judge its trustworthiness, and its value and relevance in a particular context. There are at least three dimensions that need to be evaluated. The first is called Internal validity. Internal validity refers to how well a study is performed, especially whether it avoids confounding (i.e. bias). The less chance for confounding in a study, the higher is its internal validity [21]. Tools have been developed to evaluate internal validity in different type of studies (RCTs, observational studies, etc.) [22, 23]. The second dimension is the clinical relevance, which provides an estimate of the clinical effectiveness. In this dimension are assessed outcome (surrogates vs. clinical relevant), the precision of its estimate (confidence interval) and its absolute benefit (number need to treat) [21]. The third dimension is the external validity. External validity refers to the degree to which the results of an empirical investigation can be generalized to and across individuals, settings, and times [21]. External validity can be divided into: population validity and ecological validity. The former refers to the extent to which the results of a study can be generalized from the specific sample that was studied to a larger group of subjects. The latter refers to the extent to which the results of an experiment can be generalized from the set of environmental conditions created by the researcher to other environmental conditions. For example, factors that can potentially affect external validity of a RCT could be: 1) setting of the trial; 2) selection of patients; 3) characteristics of randomised patients; 4) differences between the trial protocol and routine practice; 5) outcome measures and follow-up; 6) adverse effects of treatment [24].

1.3.4 Apply the evidence

Other key components are clinical circumstances and wishes of the patient. It is important to note that clinical circumstance can include a number of medical problems: comorbidities, concomitant therapy with several medications, etc. Indeed, the best treatment is not necessarily the one proved to be the most effective in RCTs but one that fits a particular set of individual circumstances and aligns with the patients' preferences and priority [25].

1.4 EBM in the third millennium

Before EBM, consensus meetings were a common method for determining whether treatments were useful. Now EBM requires experts to systematically and transparently appraise the evidence upon which their recommendations are based [13]. However, EBM is facing new challenges. One of this is represented by the hidden bias caused by conflict of interest [26] In 2006 Heres *et al*. reviewed results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship existed between the sponsor of the trial and the drug favoured in the study's overall outcome [27]. It was found that in the 90% of the studies evaluated sponsored by a pharmaceutical company, the reported overall outcome was in favour of the sponsor's drug. This pattern resulted in contradictory conclusions across studies when the findings of trials of the same drugs, but with different sponsors, were compared [27]. One of the methodological reason why industry-sponsored studies might be more likely to reveal a benefit of their drug is publication bias, *i.e.* positive results are more likely to be published than negative results[13, 28]. This problem is also exacerbated by duplicate publications. In 1997 it was conducted a systematic review and meta-analysis of RCTs investigating ondansetron's effect on postoperative emesis to quantify the impact of duplicate data on estimates of efficacy [29]. Authors found that 17% of published full reports of RCTs and 28% of the patient data were duplicated. The Inclusion of duplicated data in meta-analysis led to a 23% overestimation of ondansetron's antiemetic efficacy [29].

Bias related to the entering and analysing of data can be another methodological reason why industry-sponsored studies could be more likely to reveal a benefit of their drugs [13]. In a study performed in 1996 the reports of 196 trials comparing new NSAIDs with established NSAIDs were analysed, finding that the new drugs were five times more likely to appear more effective than the established one [30]. Where possible, the Author reanalysed the data and found that the choice of dose, multiple comparisons, wrong calculation, subgroup and within-groups analyses, wrong sampling units, change in measurement scale before analysis, baseline difference, and selective reporting of significant results were some of the verified or possible causes for the large proportion of results that favoured the new drugs[30].

Improving health outcomes do not include only EBM. Economy and social factors seems indeed to play an important role [13]. Furthermore, in parallel with the development of EBM, the Quality Improvement (QI)[31, 32] developed to address similar problems, but with a focus on recurrent problems within systems of care. EBM and QI have similar aims but focus on different parts of the

problem. EBM focuses in particularly on doing the right things, i.e. actions informed by the best available evidence, whereas QI focuses more on doing things right, i.e. being sure that the proposed actions are done thoroughly, efficiently and reliably. Indeed, EBM and QI can be viewed as complementary helping to how to do the right things right [33, 34].

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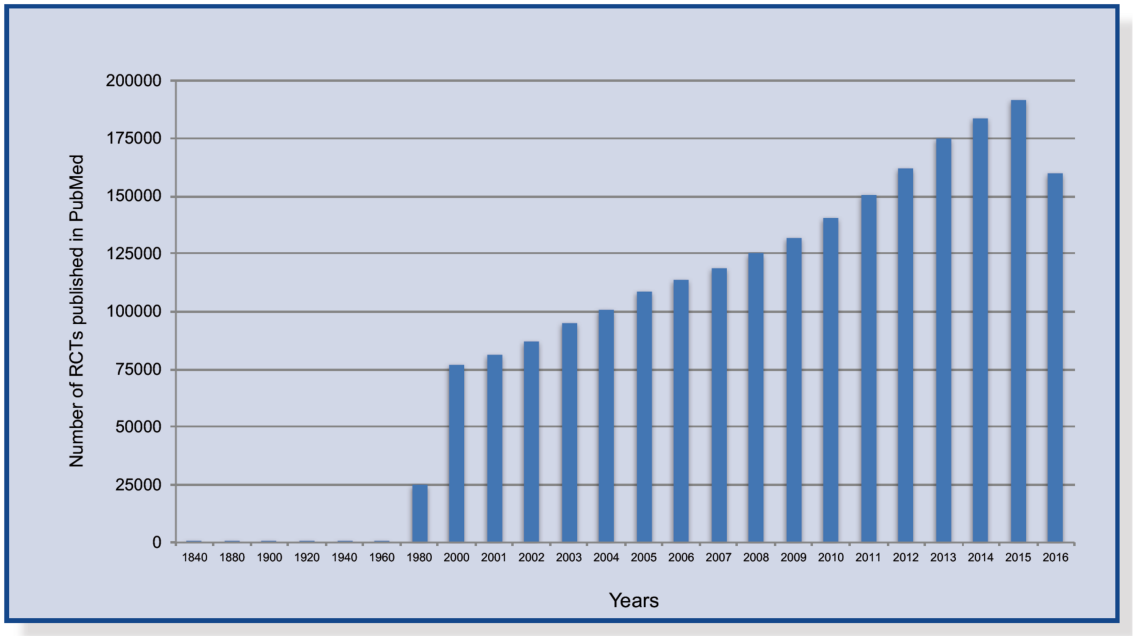
2 Systematic Review and Meta-Analysis

2.1 Decision in Health Care

Early last century, physicians had small range of possible diagnoses, few simple tests, and very few treatments (most ineffective) to choose from [1]. The first edition of Merck Manual (1899)[2] had just 192 pages. In the 1999, the centennial edition of the manual was made up of 2833 page [3], due to the incredible progress made in the field of pathophysiology, diagnosis, and therapy. In some case, new treatments have almost eliminated some diseases (e.g. smallpox), while in other have significantly improved the outcome. However, many treatments could be defined "*half-way technologies*[1], that is treatments that improve but not cure a condition (e.g. several oncological therapies). Consequently, health-care decisions have become very complex

Indeed, decisions in health care are particularly awkward [4], as they involve a complex web of input and uncertainties. It is necessary to draw information from many sources: primary data, preference of patients, clinical experiences, personal opinions, medical and legal rules, scientific evidence. Furthermore, this mix of inputs can vary depending from the type of clinical issue, the available data in that particular period, and the decision makers. Nevertheless, the *weight* of the scientific evidence has become increasingly important [5]. Unfortunately, the *number* of the evidence is also increasing dramatically. For example, as shown in **Figure 2.1.1**, the number of RCTs increased from about 40 in the 1930s to nearly 200,000 in 2015. This makes scientific updating extremely difficult. Indeed, doctors, nurses, managers need to remain updated about multiple topics. Scientific publications on the effectiveness of a treatment, if taken individually or in small groups randomly selected, can present confusing results and, in some cases, even contradictory. Therefore, to establish the efficacy, the safety, and the utility of a health-intervention is necessary to perform a review of the literature to get an update and overall assessment (even if not final) of the health-intervention evaluated.

Figure 2.1.1 Numbers of RCTs published in PubMed from 1840 since November 2016.



2.2 History of Reviews in Science

Efforts to produce reviews of researches are not new. More than 3 centuries ago, two English-language journals - namely *Weekly Memorials* and *Medicina Curiosa,* both established in 1684 - contained abstracts of articles and/or books published elsewhere [6, 7]. Between 1752 and 1798, a periodical called *Commentarii de Rebus in Scientia Naturali et Medicina Gestis* was published in German. It consisted of abstracts from scientific and medical books [8]. This periodical became a model for the first journal of abstracts of books published in English in 1773 in Edinburgh, called *Medical and Philosophical Commentaries* [9]. This journal published critical appraisals of important new books in medicine, including, for example, William Withering's now classic *Account of the foxglove* [10] on the use of digitalis for treating heart diseases[11]. Coming to the last century, social sciences, and in particular psychology and educational research, developed an early interest in the synthesis of research findings. 80 experiments assessing the *potency of moral instruction in modifying conduct* were reviewed in 1933

[12]. In 1972, Archie Cochrane, a British epidemiologist, drew attention to the fact that there were no ready access to reliable reviews of the available evidence for who wanted to make informed decisions about health care [13]. Since 1974, he began to systematically identify and assembly in a trial register all controlled studies in perinatal medicine. By 1985, the register contained more than 3500 reports, allowing the preparation of almost 600 systematic reviews in the late 1980s. One year before his death (1987), Cochrane considered the collection of systematic reviews of RCTs of care during pregnancy and childbirth "*a real milestone in the history of RCTs and in the evaluation of care*"[14]. He also advised that other specialties should follow that example [14]. Some years after his death, the Cochrane Collaboration was founded with the goal to improve the quality of decisions in health care by "*preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of health care interventions*"[15].

2.3 Narrative Reviews

Reviews can be classified as narrative or systematic. Both must be considered as retrospective observational studies and therefore subject to systematic and random errors [16]. The quality of a review, and consequently its usefulness, depends on the extent to which scientific methods are used to minimize errors and bias. This is the most important feature distinguishing narrative reviews from systematic reviews [17].

As shown in **Table 2.3.1**, most of the narrative reviews has to do with a wide range of aspects relating to a certain topic, rather than address a particular issue in detail[18]. Moreover, the sources used to perform searches often are not specified, the search strategies (if used) are not always reported, and evaluation of the studies could not follow strict rules, resulting in a significant subjectivity in the outcome of the review. Narrative reviews are therefore often used to have a broad perspective on a given topic (e.g. narrative review on Crohn's disease can include sections on epidemiology, pathophysiology, diagnosis, etc.), or to describe innovative developments concerning fields where research is small, and characterized by few preliminary results coming from

studies with many limitations. Nevertheless, they are almost never useful in providing answers to specific clinical questions [16].

Table 2.3.1 Difference between narrative reviews and systematic reviews (modified from Cook et al.[16]).

Features	Narrative Review	Systematic Review
Questions	Can be broad in the aims	Usually focused on specific clinical questions
Sources and Search	Can be not specified and therefore potentially biased	Have to be comprehensive explicated and the search strategies clearly reported
Selection	Usually not specified and therefore potentially biased	Criteria have to be explicated before to begin the study and have to be uniformly applied
Appraisal	Variable	Criteria have to be explicated before to begin the study and have to be uniformly applied
Synthesis	Can have qualitative summaries	Qualitative and, where appropriate, quantitative synthesis
Inferences	Sometime evidence-based	Usually evidence-based

2.4 Systematic Reviews

Unlike the narrative reviews, systematic reviews are to be considered real research projects, that, to minimize the risks of distortions, use at each stage of the production process, a rigorous scientific methodology [19]. Indeed, guidelines have been specifically developed to help the authors to follow the best standardized methodology [20]. For these reasons, systematic review can address several important questions, as shown in **Table**

2.4.1. In **Table 2.4.2** are summarized the steps that have to be accomplished to perform a systematic review [17].

Table 2.4.1 Advantages of systematic review.

Summarize the evidence of published (and where possible unpublished) literature
Explain, if possible, discrepancies between evidence
Establish a dose-response relationship (if present)
Define the benefit-risk ratio of a health intervention
Evaluate the usefulness of diagnostic tests
Suggest or improve research hypotheses
Avoid unnecessary investigations
Support health decision makers in their choices

Table 2.4.2 Steps necessary to perform a systematic review.

Formulate a clear and precise question(s)
Define inclusion and exclusion criteria
Develop a search strategy
Establish the sources to use
Select studies
Assess study quality
Extract data
Analyze the data
If plausible from a methodological and clinical perspective, pool data
Place the results in the clinical context and compare them with the published literatures
Discuss the strengths and weaknesses of the systematic review

Firstly, it must be defined the question to which the review should answer: the usefulness of a treatment, the accuracy of a diagnostic test, the safety of a drug, etc. Then, inclusion and exclusion criteria should be defined. It was believed that systematic reviews should include only RCTs. However, this is not true. Systematic reviews can also include observational studies, especially when the evidence is scarce [21]. It is then important to established which sources (databases) to consult. In addition to conventional literature, whenever it is possible, the so-called *grey literature* - e.g. abstracts form scientific meeting - should be researched [22]. it was shown that trials

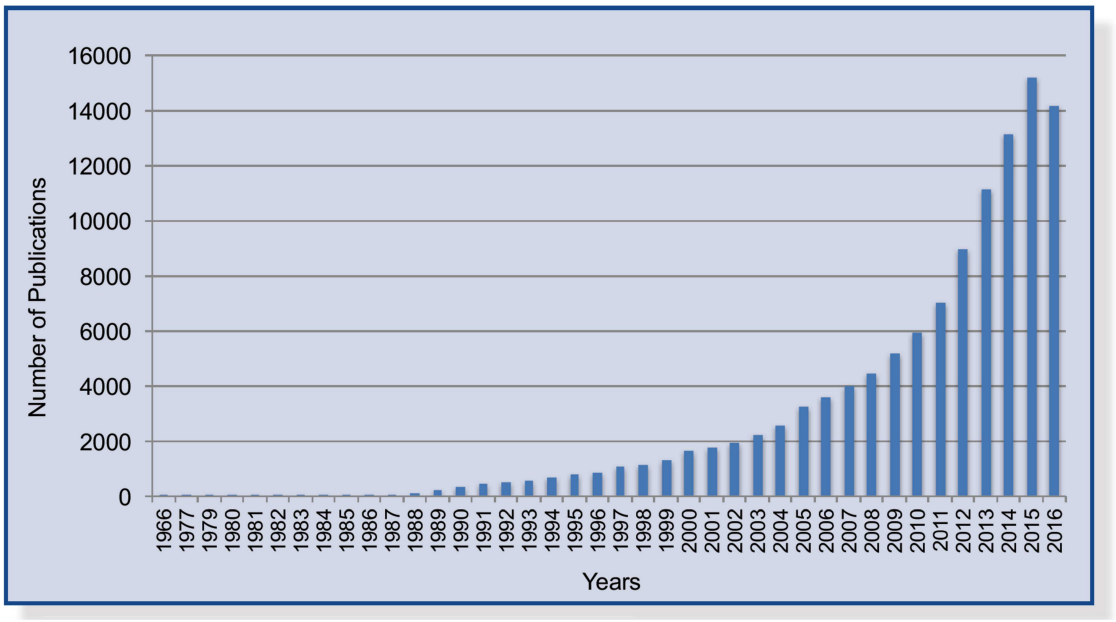
published conventionally tend to be larger and to show greater effect when compared with studies of *grey literature* [22]. Search strategy is also a key element of a systematic review. This should ideally be able to identify all the relevant studies. For relevant studies (or items), it usually meant the number of records present in the searched database(s) and that should all be retrieved. Search strategies are characterized by two elements: precision and specificity. Sensitivity is the ratio of the number of relevant records retrieved to the total number of relevant records in the database. Precision is the ratio of the number of relevant records retrieved to the total number of irrelevant and relevant records retrieved. Both are usually expressed as a percentage.[23] It is necessary to find a balance between sensitivity and precision: this task is not easy as search strategies vary with the purpose of systematic reviews. Once the studies have been identified, it is necessary to evaluate them separately to determine their eligibility based on pre-determined criteria for inclusion. The assessment of the quality of the studies is another critical issue. There are several systems of evaluations depending on the type of study. For example, at least 25 items were described for RCTs[24], although it is currently recommended the one proposed by the Cochrane Collaboration. It consists of six domains, and for each Authors must report whether there is a high, low or unclear risk of bias [25]. Afterwards, the results of the review need to be placed in the clinical context and discussed critically. Finally, it is important to emphasize the strengths as well as the potential weaknesses of the review, to give the reader an assessment as objective as possible of the evaluated health intervention.

2.5 Meta-analysis

The term *meta-analysis* was probably coined by the psychologist Glass in a paper entitled *Primary, secondary and meta-analysis of research* [26] A systematic review may or may not include a meta-analysis. A meta-analysis is a statistical analysis of the results of a systematic review, which aims to produce an estimate of health intervention

evaluated [17]. The distinction between a systematic review and meta-analysis is important because if it is always appropriate and desirable systematically review a set of data, in many cases can be inappropriate or even misleading to aggregate the data statistically. For example, in a recent systematic review of the literature about the usefulness of 5-ASA in diverticular disease, it was decided to not perform a meta-analysis as it was considered to be inappropriate [27]. The appropriateness of the execution of a meta-analysis is an even more delicate if it is considered that systematic review and meta-analysis are at the top of the pyramid of evidence [28]. The number of meta-analyses published in PudMed has soared since the period 1966-1990 (**Figure 2.5.1**), and it is widely believed that the authors of systematic reviews often find difficult to *resist* the temptation to meta-analyse even when this is questionable or clearly inappropriate [17].

Figure 2.5.1 Number of meta-analysis published in PubMed from inception since November 2016.



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3 Systematic Review and Meta-analysis for Evaluating Drug Safety: a difficult challenge

3.1 The absence of evidence is not the evidence of absence

In order to make appropriate decisions in health-care, accurate knowledge of benefit and harm of a health intervention is essential. RCTs - when well designed, conducted and reported - produce usually high quality information about the efficacy of a health intervention. In judging the effect of a treatment there are two type of errors: *type I* and *type II* [1, 2]. The *type I error* occurs when the study mistakenly found an effect that actually is not present. On the contrary, *type II error* occurs when the true effect of an intervention is missed. RCT assessing the efficacy of an intervention are based on a sample size calculated to reduce as much as possible the *type I error* (usually <5%) and, if adequately powered, reduce also the *type II error* [1, 2]. However, this type of error is a key issue when assessing potential harm of an intervention. Most of the RCTs are powered for significant benefit and not for significant harm, which make the type II error for harm much more likely. Indeed, several RCTs often conclude that the intervention is "effective and safe" but in most case this is a *biased sense of security* because of a very high *type II error* [3].

3.2 Definitions

Drug-related harm can be classified in several ways [4-7]. For the sake of homogeneity, it was decided to adopt the definition recently reported by the British Medical Journal[8]:

- *adverse event*: an unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it;
- *adverse effect*: an unfavourable outcome that occurs during or after the use of a drug or other intervention and the causal relation between the intervention and the event is at least a reasonable possibility;

- *complication*: an adverse event or effect following surgical and other invasive intervention;
- *harm*: the totality of possible adverse consequences (if single or multiple) of an intervention or therapy; harms are the direct opposite of benefits;
- *safety*: substantive evidence of an absence of harm; the term is often misused when there is simply absence of evidence of harm;
- *side effect:* any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment;
- *toxicity*: drug related harm; the term may be most appropriate for laboratory determined measurements, although it is also used in relation to clinical events; the disadvantage of the term "toxicity" is that it implies causality; if Authors cannot prove causality, the terms "abnormal laboratory measurements" or "laboratory abnormalities" are more appropriate.

3.3 Caveats of RCTs to evaluate drug-related harm

RCTs have several caveats affecting the assessment of adverse events (AEs) of which it is important to be aware as meta-analyses of RCTs concerning AEs will, most of the time, embrace them. Randomization should try to produce adequate comparability across the groups as every subject is as likely as any other to be assigned to the treatment (or control) group. However, RCTs are characterize by rates of discontinuation variable[9, 10] that make analysis of drug-related harm particularly complicate, especially in studies with a long-term follow-up. Blinding is another aspect that characterizes RCTs. Nevertheless, AEs can unmask the treatment assigned in particular if the comparator is a placebo[10]. Patients enrolled in RCTs are selected and do not usually reflect the real population. Therefore, individual that could be at higher risk of developing particular AEs might be missing or not adequately represented by a numerical point of view [11]. As RCTs are mainly performed to assess the efficacy of a health intervention, they are not powered to evaluate its safety. For this reason, often systematic and planned method of AEs collection are not performed. On the other hand, it should also not be forgotten

that in several case AEs are unpredictable, making an *a priori* establishment of tools to detect these events challenging[12]. RCTs may not report all AEs, being silent on some of them considered trivial by Authors [13]. As a consequence, information about a relatively increase in modest, but potentially clinically relevant AEs could not be detected[14]. RCTs can also lack of data on the frequency, severity, or timing of AEs in relation to drug exposure, determining additional problems to characterize the safety profile [15]. AEs are often collected during study's visits and this could determine a patient's inability to remember timing of AE occurrence. However, even when information of timing of AEs is available, there should be caution in the interpretation of data. For example, it could happen that there is an initial increase in AEs followed by a decreasing. This may be interpreted as a lower risk of AEs in the long term. However, the reduction of AEs over time could simply reflect the reduction of the number of patients available in the cohort followed-up (a phenomenon more pronounced in studies with long follow-up). This problem become more critical when the outcome assessed is rare [16]. Finally, the lack of adherence to assigned treatment may bias AE assessment, the extent and the direction depending on the association between drug adherence and occurrence of the AEs[10]. In some cases, it could happen that patients failing to adhere to the allocated treatment could be sicker due to their comorbidities, putting them at higher risk for development of AEs. On the other hand, lack of adherence could just represent a poor tolerance to the assigned treatment and therefore a higher susceptibility to AEs. Finally, if the lack of adherence related to all group of a trial, this could mask the association between the study drug and related AEs.

3.4 Systematic Reviews and Meta-analyses of Adverse Events

In principle, the steps to follow to perform a systematic review (and if *appropriate* a meta-analysis) of adverse effect are similar to those used (and previously described) for systematic review and meta-analysis of beneficial effects. However, some of those steps

can be different. One of these has to do with the type of AEs to be included. The selection of adverse outcome(s) to include in a review is not a simple choice. Some AEs associated with a health intervention may be well known whilst others will not. In general, there may be two strategies[4]: a narrow and a broad focus. The former evaluates only few (often the most serious) AEs. The pros are an easier approach, and more likely to obtain significant results that could significantly impact the health practice. The major con is that this strategy can be adopted only for AEs known in advance. The latter approach ca be used to assess multiple AEs, whether known or previously unrecognized. The pros of this method are wider coverage, and discovery of new AEs never that were known. The major con is that this approach is very resource-consuming (time, personnel, money, etc.), with the risk of get few useful information. Clearly, the approach has to be tailored, as much as possible, according to the specific aim of the review.

The type of studies to include in systematic review of AEs is an aspect around which there is a debate. Both randomized as well as observational studies can provide important data, but each design has its strengths and its limitations, as synthetized in **Table 3.4.1**[12]. Well-designed and performed RCTs yield unbiased estimates of the health intervention evaluated. However, the majority of RCTs are performed (and therefore powered) to detect a certain pre-specified difference between two potential beneficial health intervention. On the contrary they are not powered to detect AEs, determining a very high risk of type II error. Furthermore, quality of reporting AEs, reporting significantly influenced by expectations of investigators and patients, not long follow-up, and limitation to external validity (e.g. drug interaction) of the results can all biases the assessment of the AEs [12, 17-19]. Given these limitations, data coming from observational studies can be of value. Being no randomization, these types of studies can be affected by an increased risk of bias (particularly from confounding) [2, 20] However, in several cases observation studies can be the only sources of data.[4] Furthermore, there is a debate to clarify if controlling for confounding by indication for unanticipated AEs really useful. Indeed, it has been argued that confounding is less likely to occur when

outcomes are unintended or unanticipated than when outcomes are an intended effect of the exposure.

Table 3.4.1 Pros and Cons of different design of studies to assess adverse effects of healthcare interventions (modified by[12]).

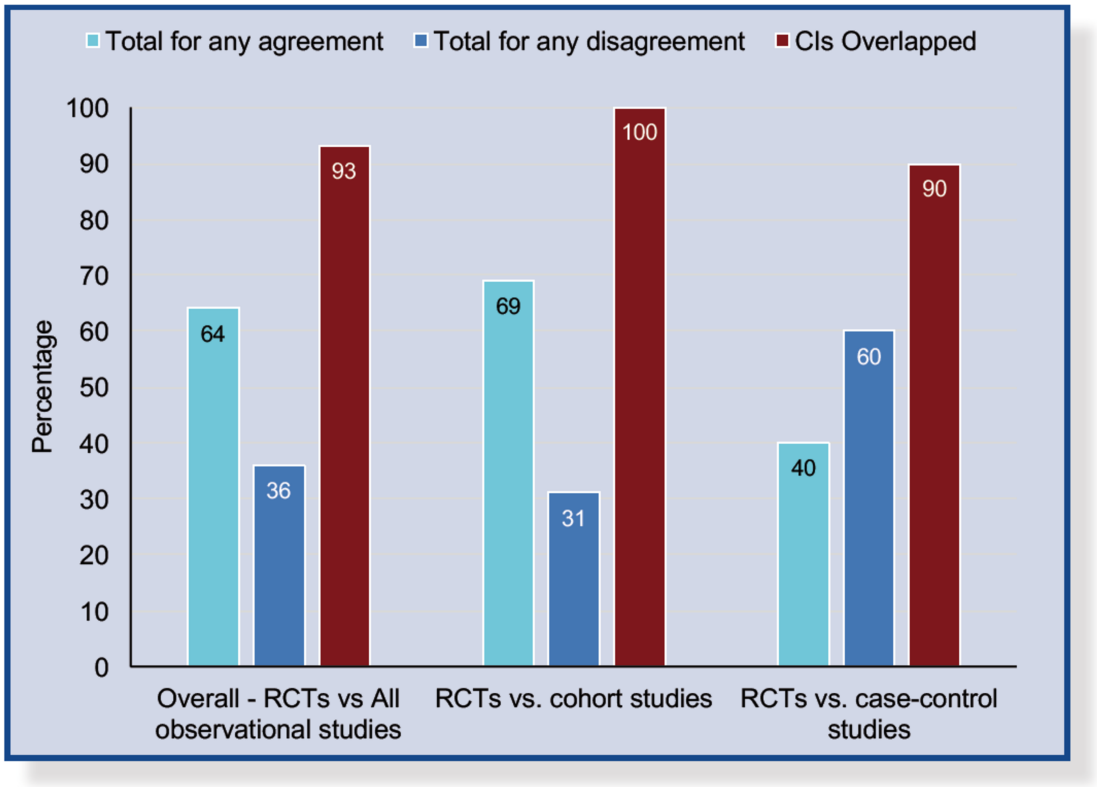
Type of Study	Pros	Cons
Spontaneous reporting	Detect a wide range of events	Absence of denominator or control group, making difficult to quantify the risk
	Useful for recognize signals of rare (low background incidence in treated population) and/or unexpected events (e.g., new not recognized pathologies)	Data (e.g. format and type) differs substantially among regulators
	Statistical techniques have been implemented for signal detection	Clinical features may be partial, causality not clear
		Selective reporting or under-reporting of cases
RCTs	Randomization reduces possibility of confounding at baseline	The recruitment criteria can determine the exclusion of patients who are at risk of developing AEs
	For known AEs it can be possible to prospectively arrange a specified monitoring	Most of the time not powered for detection of significant difference between groups for AEs
	Intervention is usually well specified	
Non-randomized studies	Data coming from patients much more much more similar to those seen in clinical practice and with longer follow-up	Monitoring for rare or unexpected events could be less rigorous, and the length of follow-up could be no sufficient to identify problems
	Case control designs could have as primary outcomes rare events	Design of study susceptible to confounding
	Could evaluate dose and duration and/or dose relationship as well susceptibility factors of patients	Exposures to drugs often based on computerized records rather than dispensing or actual use

This is because the potential for AEs are not usually associated with the reasons for choosing a particular treatment, and therefore could not influence the prescribing decision [21-23].

According to the Cochrane Adverse Effects Methods Group, three strategies can be used to address AEs[4]. The first strategy is based on assessing the benefits and risks of a health intervention using the same methodology, and applying the same inclusion and exclusion criteria. The second strategy is to use different eligibility criteria for selecting studies that address AEs compared with studies assessing beneficial effects. The third strategy is to perform a separate review of adverse effects alone. Each strategy can have its advantages and disadvantages and therefore need to be customized according to the specific aim of the review.

Until a short time ago, it was unknown if different study designs could provide consistent findings about AEs or if the outcomes were so different that it would be no appropriate to combine them in a single review. A meta-analysis of meta-analyses[23] aimed to assess this question and, as shown in **Figure 3.4.2**, found that the estimates of harm from meta-analyses of the different study designs had 95% confidence intervals that overlapped in a high percentage (93%).

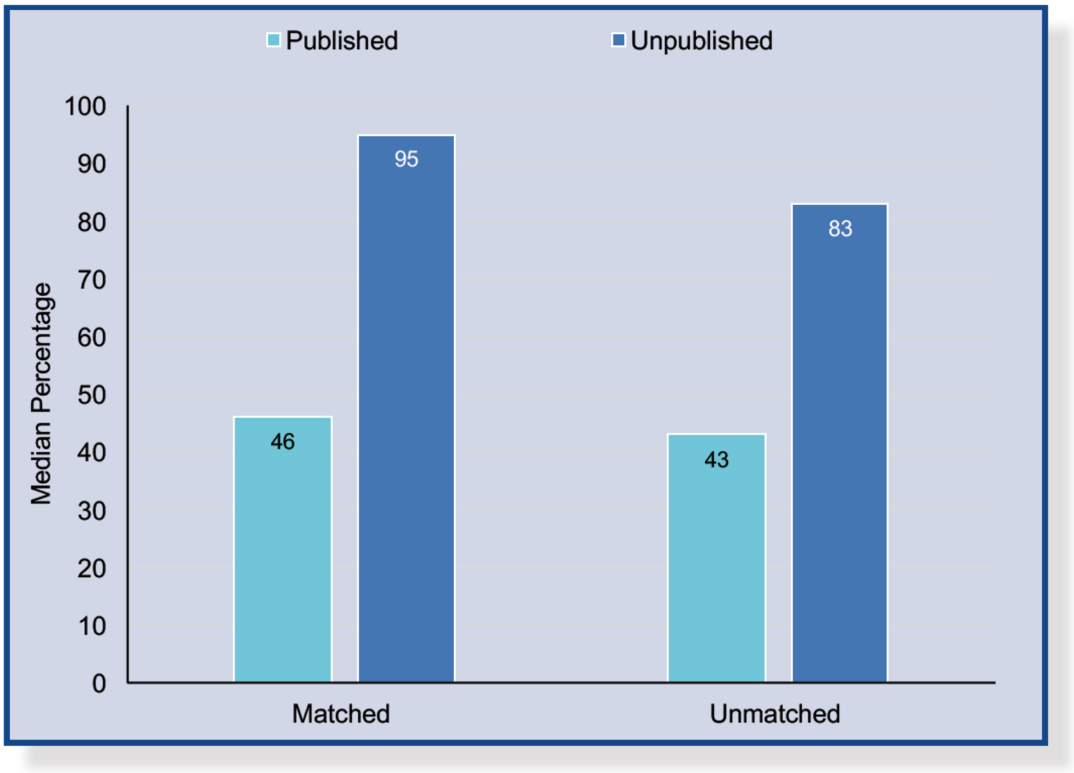
Figure 3.4.2 Agreement, disagreement and overlap of confidence intervals between meta-analysis for harms of RCTs vs. observational studies.



In the 64% of cases the results agreed (both studies showing a significant increase or significant decrease or both showing no significant difference) and there was less discrepancy between the study designs in meta-analyses that generated more precise estimates (i.e. had larger population included), either because of better quality, or because the populations were more similar (perhaps because large, long-term RCTs capture a broad population similar to observational studies)[23]. Another critical issue is represented by the unpublished studies. Unpublished studies mean[24] data that could be located through any other source (e.g. websites, trial registries, industry contact, or personal contact) and including "grey literature," defined as print or electronic information not controlled by commercial or academic publishers (e.g. government reports, working papers, press releases, theses, and conference proceedings, etc.). As

shown in **Figure 3.4.3**, a recent systematic review[24] found that he median percentage of published documents with adverse events information in matched studies (i.e. different version of the same study) were 46% and 95% for published and unpublished studies, respectively.

Figure 3.4.3 Difference between published and unpublished studies in reporting harms.



There was a similar pattern in unmatched studies (i.e. separate set of studies in the same topic area), for which 43% of published studies contained adverse events information compared to 83% of unpublished studies[24]. The Authors therefore stressed the concept that *"it will not be possible to develop a complete understanding of the harms of an intervention unless urgent steps are taken to facilitate access to unpublished data"*.

If a meta-analysis is performed, caution should be made concerning the choice of statistical method to pool data. Generally, it is advised to use relative scale as absolute risk model are unpowered and result in type II error[12]. In the context of AEs,

heterogeneity is important but of lesser concern if the analysis is dealing to see if there are rare but serious adverse events. The Peto odds ratio provides the best confidence interval coverage, and is more powerful and relatively less biased than random effects analysis when dealing with low event rates [12, 25]. To account for potential imbalance in trial size and in the number of studies with zero events, sensitivity analyses can be conducted using the fixed Mantel–Haenszel test[26]. Data coming from industry-sponsored trials can be subjected to reporting bias [27]. For this reason, obtaining data form impendent sources is important as sponsor may omit safety information from published trials[12].

3.5 PRISMA Guidelines

The PRISMA guideline to perform and report systematic review of adverse event has recently been published [8] Authors developed a checklist of 27 items (showed in **Table 3.5.1**) that should ensure a more homogeneous methodology in performing systematic reviews and meta-analysis in this field. The hope is also that this checklist can influence, indirectly, the quality of future studies dealing with the assessment of AEs.

Table 3.5.1 PRISMA Harms checklist items.

PRISMA Harms checklist items
1) Title
2) Abstract
3) Introduction
4) Objective
5) Protocol and registration
6) Eligibility criteria
7) Information sources
8) Search
9) Study selection
10) Data collection process
11) Data items
12) Risk of bias in individual studies
13) Summary measures
14) Synthesis of results
15) Risk of bias across studies
16) Additional analyses
17) Study selection
18) Study characteristics
19) Risk of bias within studies
20) Results of individual studies
21) Synthesis of results
22) Risk of bias across studies
23) Additional analysis
24) Summary of evidence
25) Limitations
26) Conclusions
27) Funding

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4 Is Rifaximin Effective for the Treatment of Small Intestine Bacterial Overgrowth? A Systematic Review and Meta-Analysis

4.1 Introduction

Small intestinal bacterial overgrowth (SIBO) is a heterogeneous syndrome characterised by an increased number and/or abnormal type of bacteria in the small bowel, and it is a well-recognized cause of maldigestion and malabsorption [1, 2].

The recent discovery of an association between SIBO and functional gut symptoms, albeit controversial, has renewed interest in this mimicry. SIBO represents indeed an umbrella term, under which some different functional (e.g. irritable bowel syndrome, chronic constipation, diarrhoea) or organic (e.g. inflammatory bowel disease, coeliac disease, diverticular disease, etc.) conditions can be included, as - in each of them - bacterial proliferation (and consequent inflammation) may, at least in part, trigger similar abdominal symptoms [1].

The overall, true prevalence of SIBO - which is usually under-diagnosed - is unknown [2, 3]. Indeed, patients may not seek healthcare and SIBO may not be properly diagnosed by medical investigations. In addition, the diagnostic yield depends on the methodology adopted, so that results from different studies are difficult to compare [4, 5].

The mainstay of the SIBO treatment is based on the use of antimicrobial agents, whose aims should not be to eradicate the entire bacterial flora but rather to modify the intestinal microecology in order to get symptoms relief [1]. Ideally, the choice of antimicrobials should reflect *in vitro* susceptibility testing, but this is usually impractical because intestinal bacterial cultures need invasive methodology to collect samples under sterile conditions [6]. Therefore, hydrogen breath test (HBT) is widely used as non-invasive means to diagnose SIBO. As consequence, in clinical practice antibiotic treatment, which should cover both aerobic and anaerobic bacteria, remains primarily empiric [4-6].

Several antibiotic regimens proved to be effective over the past 50 years, with treatment

success ranging from 27% to 100% [7]. Till the end of 90', only systemic antimicrobials were used, whose adverse events and detrimental effects on gut microbiota are today well known [8]. Poorly absorbed antibiotics, unlike systemic ones, allow localized targeting of enteric pathogens and are associated with minimal risk of systemic toxicity or adverse events (AEs). The restricted use of drugs only for enteric-infections should also reduce the development of widespread resistance, especially of enterobacteria, a major limitation of current antibiotics [8].

Rifaximin is a product of synthesis experiments designed to modify the parent compound, rifamycin, in order to achieve low gastrointestinal absorption while retaining good antibacterial activity [9-11]. Both experimental and clinical pharmacology have clearly shown that this compound is a poorly absorbed antibiotic with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganism, both aerobes and anaerobes [10-13].

Rifaximin fulfils all the characteristics set by DuPont and Ericsson [14] for the ideal antimicrobial that should be used for the treatment of gastrointestinal infections (including dysbiosis and SIBO). As a consequence, over the past decades, rifaximin has been largely used to treat SIBO [1, 7] even if there is currently a lack of a critical summary of evidence. To bridge this gap, a systematic review and meta-analysis of randomized and non-randomized studies was performed to evaluate the clinical effectiveness of and safety rifaximin to eradicate SIBO in adult patients.

4.2 Methods

4.2.1 Search strategy and study selection

This meta-analysis was developed according to the PRISMA [15] and to the MOOSE [16] statement guidelines. A search of the medical literature was conducted using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Scopus and Web of Science from inception to March the 16th 2015. Detailed eligibility criteria for study inclusion are provided in **Table 4.2.1**. The search strategy had two sets of terms joined together with the "AND" operator. The first included the condition of interest: *small intestine, intestinal diseases, bacteria, bacterial infections, blind loop syndrome, breath tests, glucose, lactulose, xylose, sucrose, irritable bowel syndrome* (both as Medical Subject Heading terms and free text term), and *small bowel bacterial overgrowth, small intestine bacterial overgrowth, SIBO, small bowel, small intestine, malabsorption, syndromes, IBS, functional diseases, hydrogen breath test, glucose breath test, lactulose breath test, xylose test, sucrose breath test, jejunal aspirate* (as free text term). The second included the treatment evaluated: *rifaximin (*as subject heading and free text term in Embase and as free text term in the other databases). A search of the abstract books from the Digestive Disease Week (2000–2014), American College of Gastroenterology (2004-2014), United European Gastroenterology Week (2000 – 2014), British Society of Gastroenterology (2001-2014), and Asian Pacific Digestive Week (2003 – 2014), was also performed. Bibliographies of all identified relevant studies were used to perform a recursive search. There were no language restrictions. Abstracts of the papers identified by the initial search were evaluated independently and in a blinded manner by the two authors for appropriateness. The primary outcome was to assess the efficacy of rifaximin to eradicate SIBO, and the secondary outcome was to evaluate its safety.

Table 4.2.1 Inclusion Criteria.

Inclusion Criteria
RCTs and observational studies using rifaximin to eradicate SIBO
Patients aged ≥ 18 years
Test to diagnose SIBO reported
Criteria to consider a test positive for SIBO reported
Follow-up performed to assess eradication
Rifaximin regimens reported*
Studies not including patients with neoplastic diseases

*, studies using cyclic treatment of rifaximin or reporting more than one dosage of rifaximin tested but not indicating the number of patients treated with each dosage were not included.

4.2.2 Data Extraction

The 2 reviewers independently extracted data concerning the efficacy and the safety of rifaximin using pre-designed data extraction forms, as dichotomous data. In addition, the following clinical data were extracted for each trial: rifaximin regimen (dose and duration), type of study (randomized controlled trial (RCT), cohort studies, etc.), type of test used to diagnose and follow-up SIBO, sample size, time between end of treatment and eradication assessment (follow-up), country where the study was carried out, concomitantly use of fibre, mesalazine, pre or probiotics, AEs, whether the study was performed in a gastrointestinal (GI) setting, and if presence of irritable bowel syndrome (IBS) was specifically assessed. Finally, the studies reporting lower GI symptom assessment before and after treatment with rifaximin were identified and evaluated. Any disagreement was resolved by discussion between the two Authors. Distinction between cohort and case series was made according to the definition provided by Dekkers and co-workers' [17]. Risk of bias for RCTs was assessed as described in the Cochrane handbook [18]. The Newcastle–Ottawa scale (NOS, possible highest score: 9) was used to assess the quality of case-control studies if included [19]. Cohort studies and case series were evaluated using the 20-items quality appraisal checklist developed by the Institute of Health Economics (IHE, Canada) [20].

4.2.3 Data Synthesis and Statistical Analysis

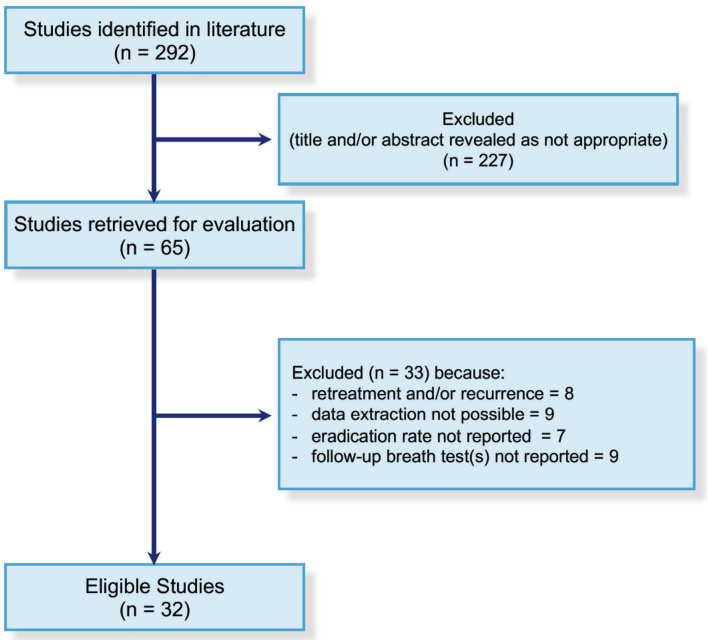
Data for primary and secondary outcomes were pooled from all kinds of studies using a random effects model as there is generally no reason to assume that trials included in the analysis are identical in the sense that the true effect size is exactly the same in all the studies [21, 22]. In case of cross-over studies, data from first and second period were combined, if possible. Intention to treat analysis (ITT) was adopted where possible. To obtain an estimate of the maximum potential benefits, a per protocol analysis was also performed [23]. Where possible, data from RCTs were pooled using a random effects model [21], results expressed as relative risk (RR) for success of SIBO eradication, and number need to treat (NNT) calculated as described in the Cochrane handbook [24]. Heterogeneity between trials was assessed by χ^2 test for heterogeneity, and I^2 statistic with 95% CIs was also calculated [25]. Its value ranges from 0% to 100 %, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value below 25 % was chosen to represent low levels of heterogeneity [25]. When the degree of statistical heterogeneity was greater than this cut-off, for both primary and secondary outcomes, possible explanations were investigated with meta-regression and sub-group analysis using the residual maximum likelihood with random effects weighting and the Knapp and Hartung t-distribution [26]. Prior to analysis, adjusted proportions were calculated using a logit transformation [27]. For the primary outcome, only studies where intention to treat analysis was possible were considered, and the covariates used in meta-regression and sub-group analysis were: a) duration of treatment; b) dosage of rifaximin; c) type of study (dichotomised as RCT or no-RCT); d) type of test used to diagnose and follow-up SIBO; e) sample size of the study (dichotomised as ≥ 50 patients vs. < 50 patients; f) time between end of treatment and eradication assessment categorised as: within 7 days after the end of treatment; within 2-4 weeks after the end of treatment; and > 4 weeks after the end of treatment; g) country where the study was performed (dichotomised as Italy vs. not Italy since most studies were performed in this Country); h) concomitantly use of fibre, mesalazine, pre or probiotics (dichotomised as not concomitant use vs. concomitant use). For the

secondary outcome, covariates used in meta-regression and sub-group analysis were a) duration of treatment; b) dosage of rifaximin; c) type of the study; d) sample size of the study; e) country where the study was performed; f) concomitantly use of fibre, mesalazine, pre or probiotics. We also performed a sub-group analysis to evaluate the eradication rate in patients with IBS and in patients enrolled in extra-gastrointestinal settings (e.g. patients with diabetes, rosacea, etc.). Studies reporting lower GI symptom assessment before and after treatment with rifaximin were evaluated in order to identify those showing symptoms relief after therapy from those which did not. StatsDirect v. 3.0.165 (StatsDirect, Ltd. England) and Stata (StataCorp, 2013, Stata Statistical Software: Release 13.1 College Station, TX: StataCorp LP) were used to generate Forest plots for primary and secondary outcomes with 95% CIs, as well as Funnel plots. The latter were assessed for evidence of asymmetry and possible publication bias or other small study effects using the Egger's linear regression [28]. Stata and Comprehensive Meta-Analysis v. 3.3.070 (Biostat, Inc., Englewood, NJ) were used to perform meta-regression analyses.

4.3 Results

The search strategy employed identified 292 citations, 227 of which were excluded after examining title and abstract. There was a total of 65 studies that were retrieved and evaluated in more detail. Of these, 33 were excluded for various reasons, leaving 32 studies [29-60] (2 of which were abstracts [36, 54]) that were eligible for inclusion involving 1331 patients as shown in **Figure 4.3.1**. 24 studies were cohort studies [29, 32, 33, 35-37, 39-43, 45, 46, 49, 50, 52-60], 7 randomized controlled trials (RCTs) [30, 31, 34, 44, 47, 48, 51]. Finally, 1 study was a randomized cross-over study [38]: since all patients received rifaximin (before or after placebo), they were all included in the proportion meta-analysis for pooled eradication rates and pooled adverse events rate. In 2 studies rifaximin was used in patients under mesalazine therapy [30, 35], in other 2 studies rifaximin was given to patients taking also fibres [38, 51], and in 1 study it was employed in association with probiotics [37].

Figure 4.3.1 PRISMA Flow Diagram of the Systematic Review.



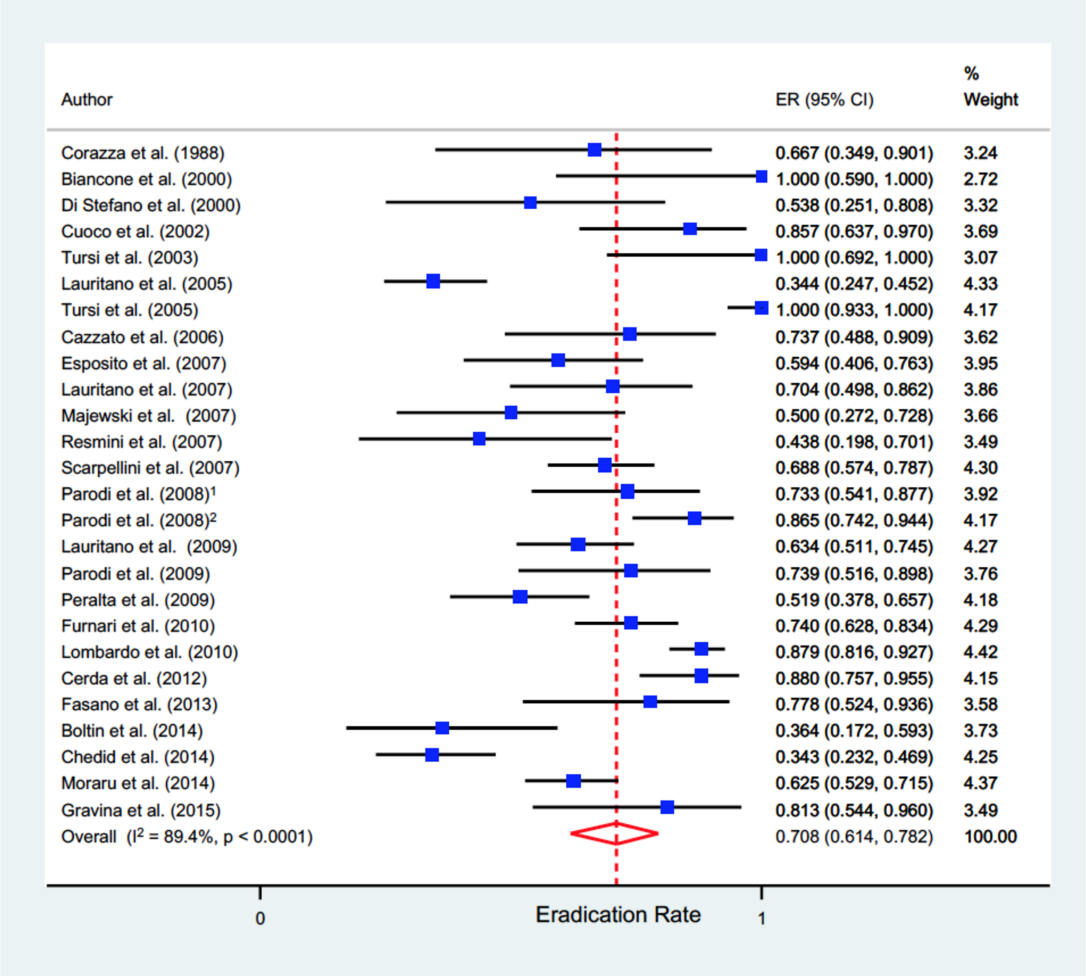
The glucose hydrogen breath test (GHBT) and the lactulose hydrogen breath test (LHBT) were used to diagnose and follow-up SIBO in 17 (53.1%) [30, 31, 34, 36, 37, 40-42, 44, 48, 49, 51-54, 59, 60], and 13 studies (40.6 %) [29, 32, 33, 35, 38, 39, 43, 45, 46, 50, 55, 57, 58] respectively. 2 studies [47, 56] used both breath tests to identify SIBO. However, only one [56] of those assessed also eradication by combined GHBT and LHBT. Doses of rifaximin used ranged from 600 mg/die to 1600 mg/die, and duration of treatment ranged from 5 to 28 days. 75% of the studies were performed in Italy. Detailed characteristics of studies included in the meta-analysis are provided in Supplementary Tables and Figures (from **Table 4.5.1 to Table 4.5.3**). No RCT was at low risk of bias (**Table 4.5.4** Supplementary Tables and Figures). Quality cohort studies ranged between 10/20 and 18/20, according to quality appraisal checklist developed by the IHE [20] (from **Table 4.5.5 to Table 4.5.9** Supplementary Tables and Figures). ITT evaluation was possible in all but 6 studies [37, 38, 41, 45, 52, 55].

4.3.1 Overall eradication rates

4.3.1.1 Intention to Treat Analysis

Intention to treat analysis was possible in 26 studies [29-36, 39, 40, 42-44, 46-51, 53, 54, 56-60] including 1141 patients. The pooled eradication rate of SIBO was 70.8% (95% CI: 61.4 to 78.2; **Figure 4.3.2**) with evidence of significant heterogeneity (Cochrane Q: p<0.0001; I^2 = 89.4%; 95% CI: 86.1 to 91.6), and Funnel plot asymmetry (Egger test: -4.16; 95% CI: -6.40 to -1.93; p<0.0001, **Figure 4.5.1** Supplementary Tables and Figures).

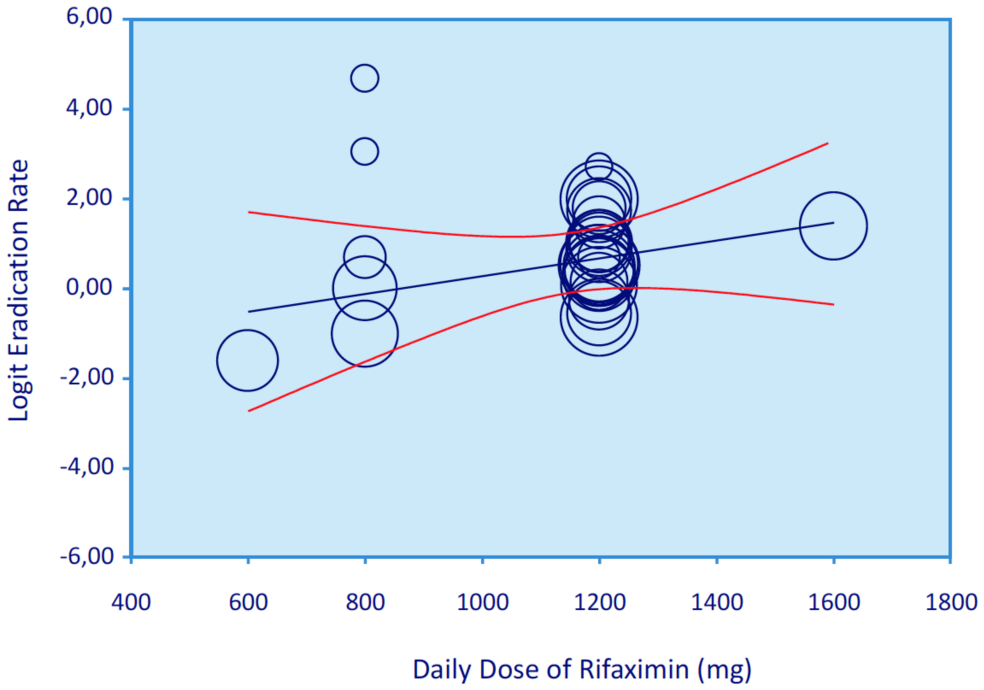
Figure 4.3.2 Forest Plot of SIBO Eradication Rate According to ITT Analysis.



ER, eradication rate.
1, ref; 46; 2, ref. 47.

Being only two the studies where both breath tests were used [47, 56], these were not included in the regression and sub-group analysis. Meta-regression showed that eradication significantly increased for unit increase in dosage of rifaximin (**Figure 4.3.3**), in non-RCTs, and in studies where fibres, mesalazine, pre or probiotics were concomitantly used with rifaximin (**Table 4.5.10** Supplementary Tables and Figures). A sub-group analysis was also performed according to the same variables used for the meta-regression analysis (**Table 4.5.11** Supplementary Tables and Figures).

Figure 4.3.3 Meta-regression plot: Logit of Eradication Rate versus Daily Dose of Rifaximin (adjusted for all the other covariates evaluated).



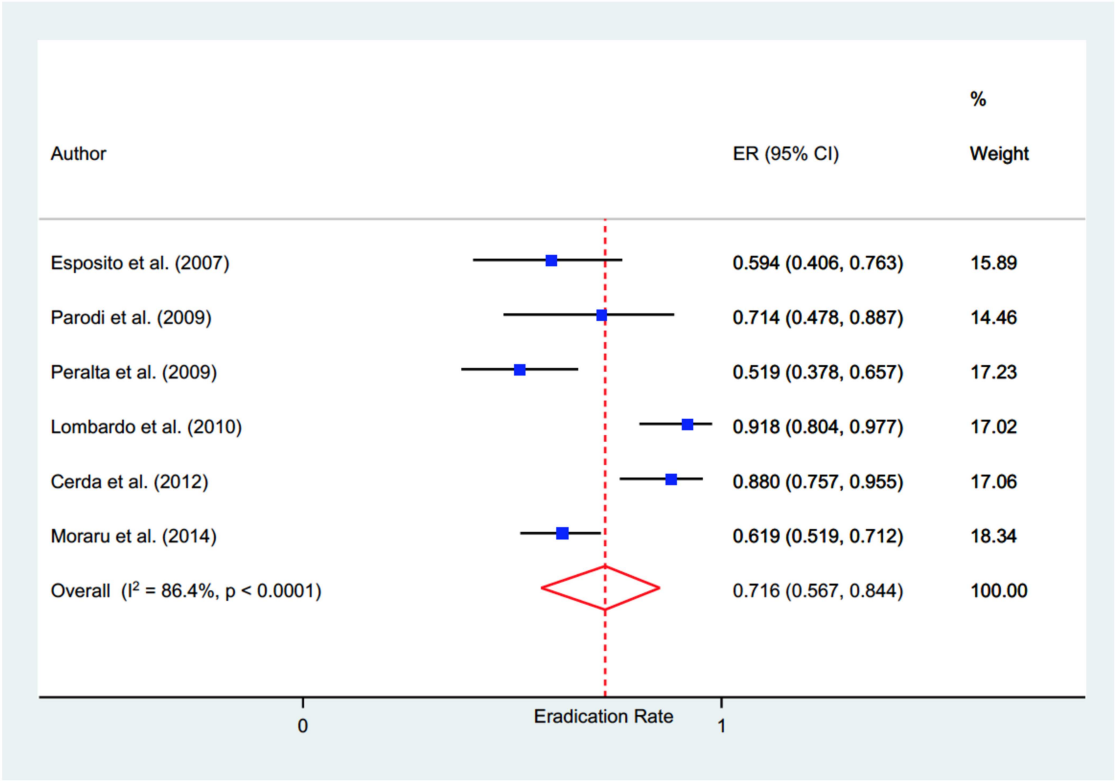
4.3.1.2 Per Protocol Analysis

The PP analysis included overall 1274 patients from all the 32 studies (the 26 studies where ITT analysis was possible [29-36, 39, 40, 42-44, 46-51, 53, 54, 56-60], and from additional 6 trials where only PP analysis could be accomplished [37, 38, 41, 45, 52, 55]). The pooled eradication rate of SIBO was 72.9% (95% CI: 65.5 to 79.8) with evidence of significant heterogeneity (Cochrane Q: p<0.0001; I^2 = 87.5%; 95% CI: 83.8 to 90.0), and Funnel plot asymmetry (Egger test: -3.47; 95% CI: -5.28 to -1.67; p=0.0005, (**Figures 4.5.2** and **4.5.3** Supplementary Tables and Figures)

4.3.2 Eradication rates in IBS patients

14 studies [37, 39, 41, 42, 44, 45, 48-50, 53-55, 58, 59] were performed in patients with IBS. In 4 of them [42, 44, 48, 58] it was not possible to extract data concerning the SIBO eradication rate, leaving 10 studies available for the analysis. Intention to treat analysis was possible in 6 studies [39, 49, 50, 53, 54, 59] involving 311 patients. The pooled eradication rate of SIBO was 71.6% (95% CI: 56.7 to 84.4; **Figure 4.3.4**) with evidence of significant heterogeneity (Cochrane Q: p<0.0001; I^2 = 86.4%; 95% CI: 70.3 to 92.0), but without evidence of Funnel plot asymmetry (Egger test: -4.80; 95% CI: -15.4 to 5.86; p=0.279, **Figure 4.5.4** Supplementary Tables and Figures).

Figure 4.3.4 Forest Plot of SIBO Eradication Rate in IBS patients According to ITT Analysis.



ER, eradication rate.

The PP analysis included overall 427 patients from all the 10 studies (the 8 studies where ITT analysis was possible plus additional 4 trials where only PP analysis could be accomplished [37, 41, 45, 55]. The pooled eradication rate of SIBO was 75.4% (95% CI: 65.0 to 84.5; **Figure 4.5.5** Supplementary Tables and Figures) with evidence of significant heterogeneity (Cochrane Q: p<0.0001; I^2 = 81.7%; 95% CI: 65.2 to 88.5), barely without evidence of Funnel plot asymmetry (Egger test: -3.73; 95% CI: -7.69 to 0.23; p=0.067, **Figure 4.5.6** Supplementary Tables and Figures).

4.3.3 Eradication rates in non-GI Settings

Seven studies [32, 40, 43, 46, 47, 56, 60] involving 182 patients were performed in non-GI settings. According to ITT analysis, the reported overall eradication rate was 74.0% (95% CI: 62.9 to 83.7; **Figure 4.5.7** Supplementary Tables and Figures) with evidence of significant heterogeneity (Cochrane Q: p=0.0149; I^2 = 62%; 95% CI: 0 to 81.4), and without evidence of Funnel plot asymmetry (Egger test: -3.61; 95% CI: -7.94 to 0.71; p=0.08; **Figure 4.5.8** Supplementary Tables and Figures).

According to PP analysis, the overall eradication rate reported was 76.8% (95% CI: 69.2 to 83.6; **Figure 4.5.9** Supplementary Tables and Figures) without evidence of significant heterogeneity (Cochrane Q: p=0.2424; I^2 = 24.5%; 95% CI: 0 to 67.9), but with evidence of Funnel plots asymmetry (Egger test: -2.62; 95% CI: -5.01 to -0.239; p=0.036; **Figure 4.5.10** Supplementary Tables and Figures).

4.3.4 Comparative Studies

4.3.4.1 Rifaximin versus Placebo

Only 1 RCT [47] compared rifaximin alone to placebo and it was performed in patients with rosacea. 87.5% (95% CI: 71.0 to 96.4) of the 32 patients randomized to rifaximin were eradicated, whilst all patient (n=20) randomized to placebo remained positive. Those were successively treated with rifaximin and the eradication found was 85.0% (95% CI:

64.0 to 94.8), giving an overall eradication rate of 86.5% (95% CI: 74.2 to 94.4). No data on AEs were reported in this study.

4.3.4.2 Rifaximin versus other antimicrobials

In two studies rifaximin (1200 mg for 7 days) was compared to chlortetracycline (333 mg t.d.s for 7 days) [31] or metronidazole (750 mg/die for 7 days) [48] respectively, including overall 168 patients. According to ITT analysis, the overall eradication rate was 61.6% (95% CI: 51.1 to 71.6) and 37.6% (95% CI: 21.1 to 55.6) in patients randomized to rifaximin and other antimicrobials respectively, with a difference in eradication rate of 24% (95% CI: 6.2 to 35.5) in favour of rifaximin. The pooled RR of eradicating SIBO was 1.50 (95% CI: 1.11 to 2.04; **Figure 4.5.11** Supplementary Tables and Figures) without evidence of significant heterogeneity (Cochrane Q: p=0.418; I^2 = 0%). Egger's test was not performed due to the low number of the studies. NNT was 5 (95% CI: 2 to 43). According to PP analysis, the overall eradication rate was 64.6% (95% CI: 53.9 to 74.6) and 42.5% (95% CI: 27.7 to 58.6) in patients randomized to rifaximin and other antimicrobials respectively, with a difference that was not significant (p=0.079). The pooled RR of eradicating SIBO was 1.53 (95% CI: 0.95 to 2.45; **Figure 4.5.12** Supplementary Tables and Figures), without evidence of significant heterogeneity (Cochrane Q: p=0.256; I^2 = 22.4%).

In the first study, there were no AEs [31]. In the second study [48], AEs were significantly more frequent in the metronidazole (22.5%; 95% CI: 14.4 to 33.5) than in rifaximin group (8.5%; 95% CI: 3.9 to 17.2; difference in AEs: 14.1%; 95% CI: 2.1 to 26). Furthermore, 6 patients (8.5%; 95% CI: 3.9 to 17.2) in the metronidazole group were obliged to discontinue the study due to the severity of AEs.

4.3.5 Combination Studies

4.3.5.1.1 Rifaximin plus fibres

In two studies [38, 51] rifaximin was given in patients taking fibres. The first one was a randomized crossover trial where patients with SIBO and symptomatic uncomplicated diverticular disease taking insoluble fibre (*i.e.* bran) were randomized to receive rifaximin or placebo [38]. The eradication rates found according to PP analysis were 83.3% (95% CI: 55.1 to 95.3) for rifaximin and 10% (95% CI: 1.8 to 40.4) for placebo with a difference in eradication significantly in favour of rifaximin (difference in eradication: 73.3%; 95% CI: 32.8 to 90.9). During the second phase of the study, patients not eradicated with placebo were treated with rifaximin reporting an eradication rate of 77.7% (95% CI: 39.9 to 97.1). The overall eradication rate (including the first and the second period) was 80.9% (95% CI: 59.9 to 92.3). AEs were not reported in details. However, no patient had to discontinue the study due to AEs of rifaximin.

The second study [51] was a RCT where patients with SIBO were randomized to receive either rifaximin alone or in combination with partially hydrolysed guar gum. The eradication rate found in the latter group was 85% (95% CI: 70.1 to 94.2) according to ITT analysis and 87.1% (95% CI: 72.5 to 95.7) according to PP analysis, and it was significantly higher than that obtained in patients treated with rifaximin alone (62.1%; 95% CI: 44.7 to 77.5 according to both ITT and PP analysis; difference for eradication rate according to ITT analysis: 22.8%; 95% CI: 3.18 to 41.5; difference for eradication rate according to PP analysis: 25%; 95% CI: 5.6 to 43.4) [51]. AEs were not reported in details. However, no patient had to discontinue the study due to AEs of rifaximin.

4.3.5.1.2 Rifaximin plus mesalazine

In two studies rifaximin was given in patients taking mesalazine. The first study was a quite small RCT [30] where patients with Crohn's disease and SIBO were randomized to receive either rifaximin or placebo. After the end of treatment, SIBO was eradicated in all patients receiving rifaximin (100%; 95% CI: 59.0 to 100), and in only 28.5% (95% CI: 3.6 to 70.9) of those randomized to placebo (difference in eradication: 71.4%; 95% CI: 23.2 to 92.1). No data on AEs were reported.

The second study was a performed in patients with acute uncomplicated diverticular disease of the colon [35] where rifaximin was able to eradicate SIBO in all patients treated (100%; 95% CI: 93.3 to 100).

4.3.5.1.3 Rifaximin plus probiotics

In one study [37] SIBO positive patients were treated with rifaximin followed by a cycle of probiotics (Lactobacilli and Bifidobacteria based preparation) for twenty-day. Follow-up was performed 4-5 months after the end of treatment and revealed an eradication rate of 82.6% (95% CI: 61.2 to 95). Treatment did not cause any significant adverse event.

4.3.6 Symptom Relief

The evaluation of studies assessing symptoms before and after treatment with rifaximin (from **Table 4.5.12 to Table 4.5.16** Supplementary Tables and Figures) showed a high heterogeneity. Indeed, the different symptoms were measured in different ways and/or, sometimes, collectively expressed as a global symptom score. Aggregating them into a meta-analysis would be not appropriate. Therefore, a thorough analysis of those studies evaluating symptoms (before and after therapy) was performed. Symptom improvement was reported in a large proportion ($\geq$ 75%) of studies, an effect seen more

frequently in studies including IBS patients (**Figure 4.5.13** Supplementary Tables and Figures).

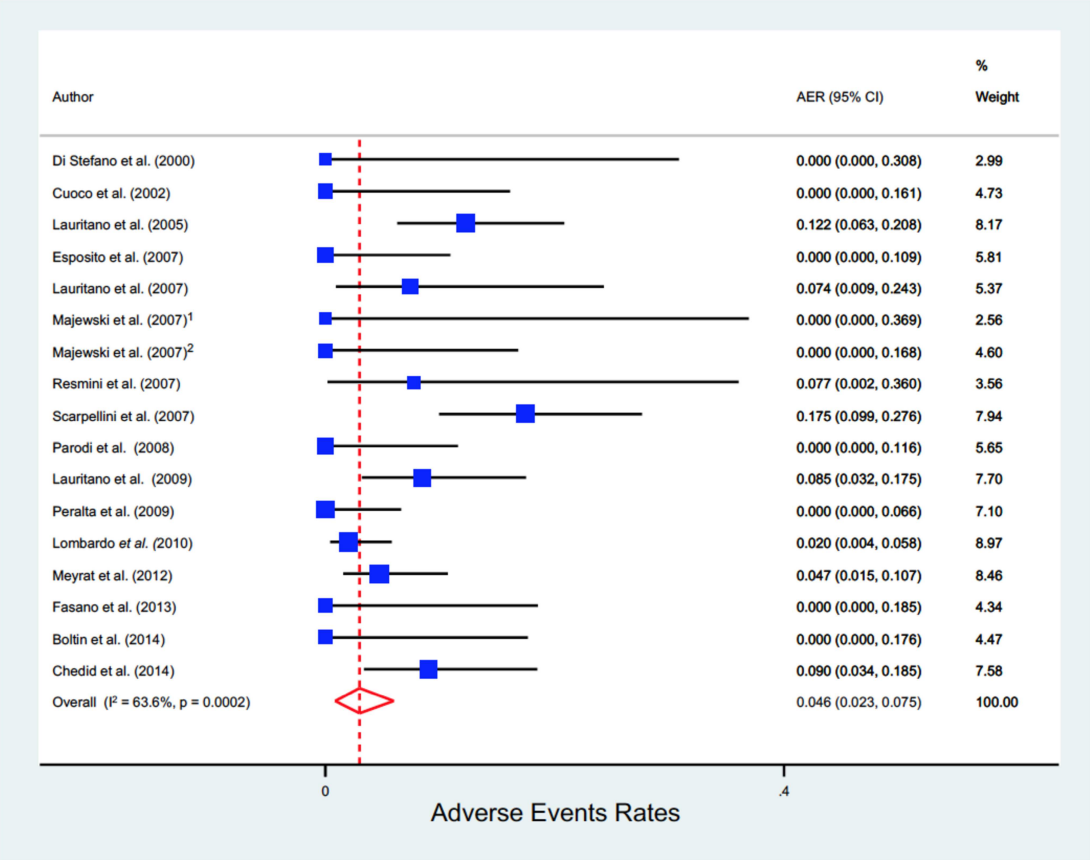
4.3.7 Adverse Events

AEs were reported in 17 studies involving 815 patients where only rifaximin was used [31, 32, 34, 39-44, 46, 48, 50, 53, 55-58]. As shown in **Figure 4.3.5**, the overall rate of AEs was 4.6% (95% CI = 2.3 to 7.5), with evidence of heterogeneity (Cochrane Q: p=0.0002; I^2 = 63.6%; 95% CI: 31.2 to 77.1), but without Funnel plot asymmetry (Egger test: 0.8794; 95% CI: -0.543 to 2.301, p = 0.2074; **Figure 4.5.14** Supplementary Tables and Figures). Meta-regression and sub-group analysis revealed that non-RCTs presented a significant lower incidence of adverse events, when compared to RCTs (Tables **4.5.17** and **4.5.18** Supplementary Tables and Figures).

Only in one study [55] the 0.47% (95% CI = 0.01 to 10.6) of patients who experience adverse events had to discontinue the therapy prematurely for this reason.

A case of *C. difficile* infection (CDI) – post treatment - was reported to occur in 1 patient of a study were rifaximin was used at the dosage of 1200 mg daily for 4 weeks. However, no information about either the time elapsed between the end of antibiotic therapy and the occurrence of the CDI or the presence of concurrent risk factors for the infection was provided [58]. The same paper reported also a case of anaphylaxis to rifaximin, again without providing any information on the severity of this adverse event.

Figure 4.3.5 Forest Plot of Adverse Events in Patients Taking Rifaximin Alone.



AER, adverse event rate.
1, ref; 41; 2, ref. 42.

4.4 Discussion

SIBO is a very heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel [3], and is becoming a common finding in clinical practice. The management of SIBO should be centred on identifying and correcting underlying causes, treating the overgrowth, and addressing the nutrition deficiencies, where detected [3, 61].

Several broad-spectrum systemic antibiotics such as fluoroquinolones, metronidazole, tetracycline, amoxicillin-clavulanic acid, chloramphenicol, *etc.*, have been used to manage SIBO [7]. However, they are usually associated to several and sometime severe adverse events [61, 62].

Rifaximin is a poorly absorbed antibiotic that has been largely used to treat SIBO over the past decades [10, 11]. Both experimental and clinical pharmacology clearly show that this compound displays a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative organisms, both aerobic and anaerobic [10, 11]. Being virtually non-absorbed, its bioavailability within the gastrointestinal tract is rather higher with intraluminal and fecal drug concentrations largely exceeding the minimal inhibitory concentration values observed *in vitro* against a wide range of pathogenic organism. Furthermore, it has been proposed that rifaximin could be able to preserve colonic flora and increase the relative abundance of Lactobacilli and Bifidobacteria, showing "eubiotic" effects [63, 64].

The results of our meta-analysis provide evidence that rifaximin is clinically effective in eradicating SIBO. A significant heterogeneity was found and multivariate meta-regression identified three covariates (namely the drug dose, the study design and co-therapy) independently associated with an increased eradication rate. Two studies reported a dose-dependent eradication rate: the higher the daily dose of rifaximin, the higher the eradication rate [34, 44]. In addition, the treatment success was significantly higher in non-randomized trials [65]. Despite RCTs are usually preferred to evaluate the efficacy of therapeutic interventions, a large amount of evidence is often accumulated through non-randomized studies. For this reason, we decided to include them in our

analysis. It is worthwhile mentioning that RCTs and non-randomized studies show a high correlation in their estimates of efficacy. However, it is more frequent to find larger treatment effects in non-randomized studies compared to than the opposite [66-68]. This was indeed the case in our study. Finally, concomitant administration of rifaximin with fibres (both soluble and insoluble), probiotics (Lactobacilli and Bifidobacteria), or mesalazine, three gut microbiota-directed therapies [69-75], consistently gave higher eradication rate. The global effectiveness of rifaximin in eradicating SIBO was maintained in the sub-group of patients with IBS, where a significant heterogeneity was still present. It is worth mentioning that the IBS studies were all non-RCTs.

The analysis of the studies including symptom evaluation points to an association between symptom improvement and rifaximin treatment. Two recent studies [76, 77] have shown that a positive H_2BT does predict antibiotic symptomatic response in patients with IBS. A thoughtful Editorial [78] actually suggested that breath testing for SIBO could represent a mean to enrich rifaximin responders amongst IBS patients. By using SIBO as a biomarker of IBS, the therapeutic gain of rifaximin over placebo, reported by the TARGET trials [79], may well be extended to reach a clinically significant figure.

All the studies included in our meta-analysis employed to diagnose SIBO (as well as to evaluate eradication) GH or LH-BT, which – although widely used - are less sensitive and specific than bacterial culture, till now considered as the gold standard [6]. Each substrate has its own advantages and disadvantages, with GHBT favouring specificity over sensitivity, while the reverse is true for LHBT [80]. However, whatever breath test is used, the effectiveness of rifaximin in eradicating SIBO remains the same, as evidenced by meta-regression analysis.

Several antimicrobials have been found effective in reducing gas production, albeit with various success rates for (*review see* [7]). However, only few head to head comparisons were performed. Conversely from our study, a recent meta-analysis on antibiotic efficacy in treating SIBO narrowed the inclusion criteria to RCTs, showing that antibiotics were more effective than placebo (OR: 2.55; 95% CI: 1.29 to 5.04) [81]. In their subsequent analysis on efficacy of rifaximin versus placebo, the Authors selected 3 RCTs, two of

which were not included in our own meta-analysis. The first trial [82] was performed in children whilst our study was devoted to adults only. The second study [83] had some methodological drawbacks. Since LHBT was performed after randomization, patients did receive treatment independently from the presence of SIBO. Additionally, two *criteria* for establishing SIBO diagnosis were used, which produced significantly different results (55% positivity with the first *criteria* versus 8% positivity with the second *criterion*). Finally, several different outcomes were adopted to evaluate rifaximin efficacy, which makes difficult to compare the results obtained with other studies.

Besides efficacy, our systematic review carefully looked at rifaximin safety and tolerability. Evidence for harms of medical interventions is important when weighting the benefits and risks of treatments in clinical decision-making. However, such evidence is often suboptimal [84, 85]. We found that 4.6% of patients treated with rifaximin reported AEs, but only the 0.47% of them had to discontinue the therapy. Meta-regression revealed that, among the covariates analysed, only non-RCTs were significantly associated with a lower rate of AEs when compared to RCTs. Although non-RCTs are considered conservative in estimating risks of harms (as it happened in our study), evaluation of a broad range (i.e. randomized as well non-randomized) of studies can help to build a complete picture of any potential harm and improve the generalizability of the analysis, without loss of validity [86].

When considering the results of this meta-analysis, several important limitations should be acknowledged. As with any systematic review and meta-analysis, the results rely on the quality and reporting of the trials. There were no studies using culture to diagnose and follow-up the eradication. We found a significant heterogeneity among trials and for this reason we performed meta-regression analysis. However, the results of this analysis are to be interpreted with caution as meta-regression has its own limitations. As it describes observational associations across trials, it can suffer from confounding. Furthermore, since the number of studies and sample size do influence the results of meta-regression, the lack of an association does not necessarily mean its “true” absence [87, 88] The associations found in a meta-regression should therefore be considered more

hypothesis-generating and not regarded as proof of causality [87, 88]. Only 25% of studies included in the meta-analysis were RCTs [30, 34, 38, 44, 47, 48, 51, 89]. No RCT resulted to be at low risk of bias, and all had problems with concealment of allocation and blinding [90]. Furthermore, for the sake of homogeneity, it was possible to pool the results of only two RCTs [31, 48]. Most of the studies included were therefore non-RCTs, which are susceptible to selection bias and, as mentioned before, tend to find larger effects. [68, 91-93]. Finally, funnel plots asymmetry suggested not only publication bias but also the presence of other types of biases, depending on other sources (e.g. heterogeneity, poor methodological quality, etc.) [94]. All the above limitations clearly affect the quality and the strength of the provided evidence and, therefore, the results of this meta-analysis should be considered with caution [95].

In conclusion, rifaximin therapy is effective and safe for the treatment of SIBO. Since the quality of the available studies is generally poor, well-designed, large RCTs (with well-established criteria to assess SIBO and related symptoms) are needed to substantiate these findings and to establish the optimal regimen (i.e. daily dose and duration) of rifaximin to treat this increasingly common condition.

4.5 Supplementary Tables and Figures

Table 4.5.1. Characteristics of the studies included in the systematic review and meta-analysis.

Authors	Type of publication and study	Country	Clinical Setting	Prior antibiotic use allowed	Test to diagnose SIBO	Criteria used to diagnose SIBO	Patients in the rifaximin arm	Dosage of rifaximin	Duration of therapy	Time of follow-up
Corazza et al.(1988)[29]	Full Paper Cohort Study	Italy	GI	nr	LHBT	Presence of a hydrogen peak > 10 ppm above the fasting level (basal value) and preceding the colonic excretion peak by at least 20 min	12	800 mg/die 1200 mg/die	5 days	1 day after EOT
Biancone et al.(2000)[30]	Full Paper RCT	Italy	GI	None within prior 1 month	GHBT	In at least one sample an H_2 level increase higher than 12 ppm when compared with minimum value before this increase	7	1200 mg/die	7 days	7 days after EOT
Di Stefano et al.(2000)[31]	Full Paper RCT	Italy	GI	None within prior 1 month	GHBT	an increase in breath H_2 excretion > 12 ppm over the baseline value within 2 hours of the ingestion of a glucose solution or an increase in breath H_2 excretion > 12 ppm in the fasting state	13	1200 mg/die	7 days	3 day after EOT
Cuoco et al. (2002)[32]	Full Paper Cohort Study	Italy	Extra GI (DM type I or II)	None within prior 3 months	LHBT	Early peak of H_2 represented by the findings of two consecutive values more than 10 ppm above the baseline values	21	1200 mg/die	10 days	1 month after EOT
Tursi et al. (2003)[33]	Full Paper Cohort Study	Italy	GI	nr	LHBT	Presence of a peak >20 ppm occurring >15 min before the colonic peak; also patients with an elevated fasting H_2 combined with an early increase in H_2 after lactulose ingestion were considered positive for bacterial overgrowth	10	800 mg/die	7 days	1 month after EOT
Lauritano et al. (2005)[34]	Full Paper RCT	Italy	GI	None within prior 1 month	GHBT	Increase in H_2 excretion >12 ppm over the baseline value within 2 hrs	90	600 mg/die 800 mg/die 1200 mg/die	7 days	1 month after EOT
Tursi et al. (2005)[35]	Full Paper Cohort Study	Italy	GI	nr	LHBT	Presence of a H_2 peak >20 ppm occurring >15 min before the colonic peak; also patients with an elevated fasting H_2 combined with an early increase in H_2 after lactulose ingestion were considered positive for bacterial overgrowth	53	800 mg/die	10 days	8 weeks after EOT
Cazzato et al. (2006)[36]	Cohort Study	Italy	GI	nr	GHBT	Increase in H_2 excretion >12 ppm over the baseline value	19	1200 mg/die	7 days	1 month after EOT
Cuoco et al. (2006)[37]	Full Paper Cohort Study	Italy	GI	nr	GHBT	At least one of the sample expired air the H_2 value was more than 10 ppm higher than baseline value	23	1200 mg/die	14 days	4-5 months after EOT
D'incà et al. (2007)[38]	Full Paper Cross-Over RCT	Italy	GI	None within prior 1 month	LHBT	Presence of an early increase (> 10 ppm above the baseline level) in H_2 after lactulose ingestion in at least two consecutive samples, or an increase in H_2 value (> 20 ppm above the baseline level) occurring ≥ 20 min after the early increase in H_2	21	1200 mg/die	14 days	within 3 day after EOT
Esposito et al. (2007)[39]	Full Paper Cohort Study	Italy	GI	No patients under antibiotic tx	LHBT	An elevated breath hydrogen concentration higher than 10 ppm over basal values	33	1200 mg/die	7 days	7 days after EOT

nr, not reported; RCT, randomized controlled trial; GI, gastrointestinal; LHBT, lactulose hydrogen breath test; GHBT, glucose hydrogen breath test; min, minutes; hrs, hours; ppm, part per million; EOT, end of treatment; DM, Diabetes mellitus.

Table 4.5.2 Characteristics of the studies included in the systematic review and meta-analysis (continued).

Authors	Type of publication and study	Country	Clinical Setting	Prior antibiotic use allowed	Test to diagnose SIBO	Criteria used to diagnose SIBO	Patients in the rifaximin arm	Dosage of rifaximin	Duration of therapy	Time of follow-up
Lauritano et al. (2007)[40]	Full Paper Cohort Study	Italy	Extra GI (Hypothyroidism)	None within prior 3 months	GHBT	Increase over the baseline of H_2 levels > 12 ppm	27	1200 mg/die	7 days	1 month after EOT
Majewski et al. (2007)[41]	Full Paper Cohort Study	USA	GI	None within prior 1 month	GHBT	A hydrogen and/or methane peak >20 ppm when the baseline was <10 ppm or in cases where the patient started with baseline of >10 ppm a further increase of >12 ppm indicated a positive result	8	800 mg/die	28 days	within 7 days after EOT
Majewski et al. (2007)[42]	Full Paper Cohort Study	USA	GI	None within prior 6 weeks	GHBT	Hydrogen and methane peak was above 20 ppm when baseline was below 10 ppm or when the patient started with baseline above 10 ppm, a further increase of more than 12 ppm was indicative of positive result	20	800 mg/die	28 days	within 7 days after EOT
Resmini et al. (2007)[43]	Full Paper Cohort Study	Italy	Extra GI (Acromegaly)	nr	LHBT	Presence of two or more distinct peaks of H_2 excretion (10 ppm compared with the basal value)	18	1200 mg/die	10 days	1 month after EOT
Scarpellini et al. (2007)[44]	Full Paper RCT	Italy	GI	None within prior 3 months	GHBT	An increase of H_2 levels over the baseline value was >12 ppm and/or CH_4 levels increased >100% with respect to the basal value	80	1200 mg/die 1600 mg/die	7 days	1 month after EOT
Yang et al. (2008)[45]	Full Paper Cohort Study	USA	GI	nr	LHBT	Hydrogen or methane values rose to more than 20 ppm at or before 90 min. of ingestion of lactulose	50	1200 mg/die	10 days	within 1 week after EOT
Parodi et al. (2008)[46]	Full Paper Cohort Study	Italy	Extra GI (Scleroderma)	None within prior 2 weeks	LHBT	Presence of two or more distinct peaks ofH_2/CH_4 excretion (>10 ppm compared to the basal value)	30	1200 mg/die	10 days	1 month after EOT
Parodi et al. (2008)[47]	Full Paper RCT	Italy	Extra GI (Rosacea)	nr	LHBT- GHBT	GHBT: a single H_2/CH_4 peak higher than 10 ppm LHBT: presence of 2 distinct peaks of H_2/CH_4 excretion (>10 ppm compared with the basal value)	52	1200 mg/die	10 days	1 month after EOT
Lauritano et al. (2009)[48]	Full Paper RCT	Italy	GI	None within prior 3 months	GHBT	Increase over the baseline of H_2 levels >12 ppm	71	1200 mg/die	7 days	1 month after EOT
Parodi et al. (2009)[49]	Full Paper Cohort Study	Italy	GI	None within prior 2 weeks	GHBT	Single H_2 peak higher than 12 ppm	23	1200 mg/die	10 days	1 month after EOT

nr, not reported; RCT, randomized controlled trial; GI, gastrointestinal; LHBT, lactulose hydrogen breath test; GHBT, glucose hydrogen breath test; min, minutes; hrs, hours; ppm, part per million; EOT, end of treatment.

Table 4.5.3 Characteristics of the studies included in the systematic review and meta-analysis (continued).

Authors	Type of publication and study	Country	Clinical Setting	Prior antibiotic use allowed	Test to diagnose SIBO	Criteria used to diagnose SIBO	Patients in the rifaximin arm	Dosage of rifaximin	Duration of therapy	Time of follow-up
Peralta et al. (2009)[50]	Full Paper Cohort Study	Italy	GI	No patients under antibiotic tx	LHBT	An early increase of H_2 concentration in the expired air higher than 20 ppm over basal values within 90 min of the oral administration of lactulose, followed by a second distinct peak after additional 15 min or more	54	1200 mg/die	7 days	3 weeks after EOT
Fumari et al. (2010)[51]	Full Paper RCT	Italy	GI	None within prior 10 days	GHBT	A single peak of H_2 excretion higher than 12 ppm was the cut-off value for test positivity	77	1200 mg/die	10 days	4 weeks after EOT
Lauritano et al. (2010)[52]	Full Paper Cohort Study	Italy	GI	nr	GHBT	Increase over baseline H_2 levels > 12 ppm	11	1200 mg/die	7 days	1 month after EOT
Lombardo et al. (2010)[53]	Full Paper Cohort Study	Italy	GI	None within prior 6 months	GHBT	Increase over the baseline H_2 level was >10 ppm	149	1200 mg/die	14 days	2 months after EOT
Cerda et al. (2012)[54]	Abstract Cohort Study	Mexico	GI	nr	GHBT	Increase over the baseline level H_2 was >10 ppm	50	1200 mg/die	10 days	EOT
Meyrat et al. (2012)[55]	Full Paper Cohort Study	Switzerland	GI	None within prior 4 weeks	LHBT	An increase in breath- H_2 concentration of at least 12 ppm above basal level was observed within 60 min of ingesting lactulose on the condition that this early rise in H_2 concentration preceded the second prolonged rise in H_2 concentration by at least 15 min	64	800 mg/die	14 days	2 weeks after EOT
Fasano et al. (2013)[56]	Full Paper Cohort Study	Italy	Extra GI (Parkinson's disease)	None within prior 1 month	LHBT & GHBT	GHBT: increase over the baseline of hydrogen levels > 12 ppm LHBT: Presence of an early increase (> 10 ppm above the baseline level within 30-60 min) in H_2 after lactulose ingestion in two consecutive samples, or an increase in H_2 value (> 20 ppm above the baseline level)	18	1200 mg/die	7 days	1 month after EOT
Boltin et al. (2014)[57]	Full Paper Cohort Study	Israel	GI	None within prior 6 months	LHBT	The test was considered positive for SIBO when an increase over the baseline level was >10 ppm	22	1200 mg/die	10 days	2 weeks after EOT
Chedid et al. (2014)[58]	Full Paper Cohort Study	USA	GI	None within prior 3 months	LHBT	A baseline breath concentration of >10 ppm for hydrogen or >7 ppm for methane only if patients were compliant with their preparation or an increase within 90 minutes (small intestine) that was followed by a larger peak (colonic), indicative of a positive study (with a decrease of at least 5 ppm following the first peak)	67	1200 mg/die	28 days	EOT
Moraru et al. (2014)[59]	Full Paper Cohort Study	Romania	GI	None within prior 4 weeks	GHBT	A clear H_2 peak, exceeding 20 ppm before the 120 minutes have passed	112	1200 mg/die	7 days	1 week after EOT
Gravina et al. (2015)[60]	Full Paper Cohort Study	Italy	Extra GI (Rosacea)	None within prior 2 months	GHBT	Increasing over the baseline of H_2 levels, was more than 12 ppm in a least two readings	16	1200 mg/die	10 days	1 & 2 month after EOT

nr, not reported; RCT, randomized controlled trial; GI, gastrointestinal; LHBT, lactulose hydrogen breath test; GHBT, glucose hydrogen breath test; min, minutes; hrs, hours; ppm, part per million; EOT, end of treatment; HGG, hydrolysed guar gum.

Table 4.5.4 Risk bias assessment of RCTs included into systematic review and meta-analysis**.**

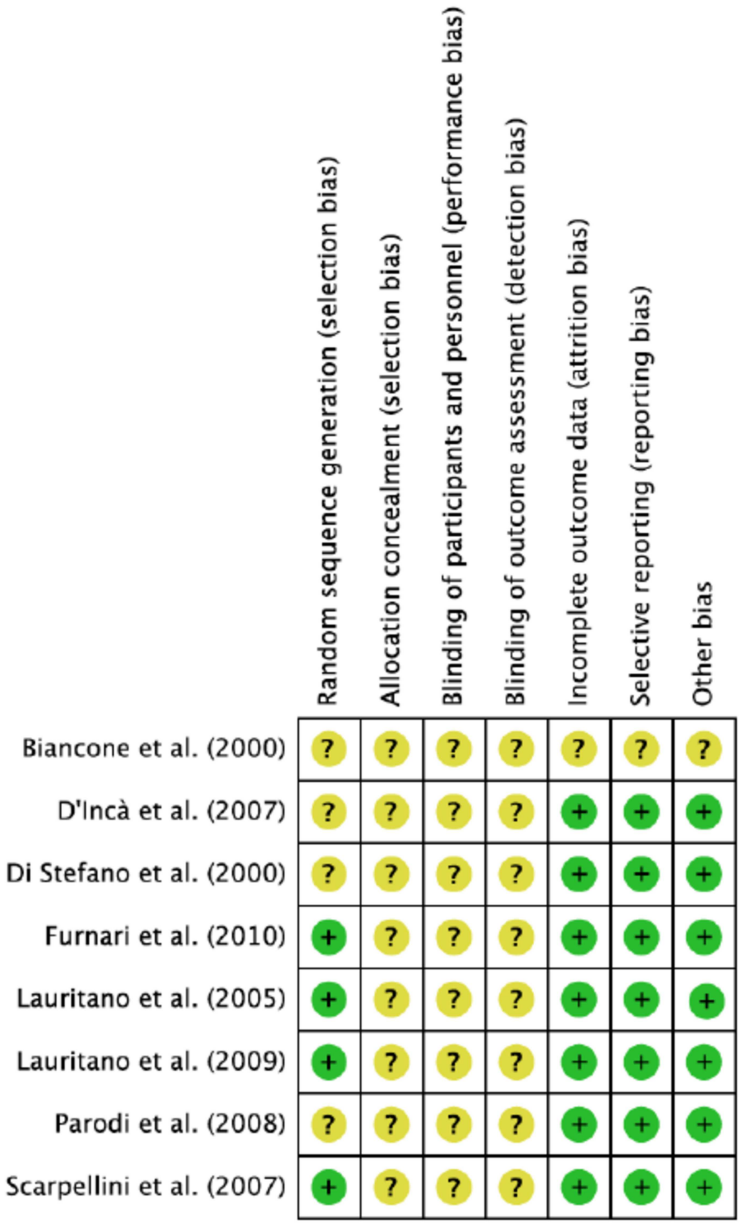


Table 4.5.5 IHE's quality appraisal checklist for cohort studies [20].

	Studies				
	Corazza et al. (1988) [29]	Cuoco et al. (2002)[32]	Tursi et al. (2003)[33]	Tursi et al. (2005)[35]	Cazzato et al. (2006)[36]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	U	U	U	Y	Y
3. Were the cases collected in more than one center?	N	N	N	N	N
4. Were patients recruited consecutively?	U	U	Y	Y	Y
Study population					
5. Were the characteristics of the patients included in the study described?	Y	Y	Y	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	P	P	Y	Y	P
7. Did patients enter the study at a similar point in the disease?	U	U	Y	Y	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	N	Y	N	Y	Y
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	Y	Y	Y	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	N	Y	N	N	N
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	N	N	N	N	N

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Table 4.5.6 IHE's quality appraisal checklist for cohort studies [20] (continued).

	Studies				
	Cuoco et al. (2006)[37]	Esposito et al. (2007)[39]	Lauritano et al. (2007)[40]	Majewski et al. (2007)[41]	Majewski et al. (2007)[42]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	N	Y	Y	U	Y
3. Were the cases collected in more than one center?	N	N	N	N	N
4. Were patients recruited consecutively?	U	Y	Y	U	Y
Study population					
5. Were the characteristics of the patients included in the study described?	Y	Y	Y	Y	P
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Y	Y	Y	Y	Y
7. Did patients enter the study at a similar point in the disease?	U	U	N	U	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	Y	N	Y	N	N
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	Y	Y	N	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	N	Y	Y	Y	Y
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	N	N	Y	N	N

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Table 4.5.7 IHE's quality appraisal checklist for cohort studies [20] (continued).

	Studies				
	Resmini et al. (2007)[43]	Yang et al. (2008)[45]	Parodi et al. (2008)[46]	Parodi et al. (2009)[49]	Peralta et al. (2009)[50]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	Y	N	Y	Y	Y
3. Were the cases collected in more than one center?	N	N	N	N	N
4. Were patients recruited consecutively?	U	Y	Y	Y	U
Study population					
5. Were the characteristics of the patients included in the study described?	Y	N	Y	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Y	Y	Y	Y	Y
7. Did patients enter the study at a similar point in the disease?	N	U	N	U	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	Y	N	Y	N	N
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	U	Y	Y	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	Y	N	Y	N	Y
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	Y	Y	Y	Y	N

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Table 4.5.8 IHE's quality appraisal checklist for cohort studies [20] (continued).

	Studies				
	Lauritano et al. (2010)[52]	Lombardo et al. (2010)[53]	Cerda et al. (2012)[54]	Meyrat et al. (2012)[55]	Fasano et al. (2013)[56]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	U	Y	U	Y	Y
3. Were the cases collected in more than one center?	N	N	U	N	U
4. Were patients recruited consecutively?	U	Y	U	Y	Y
Study population					
5. Were the characteristics of the patients included in the study described?	P	Y	P	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	P	Y	P	Y	Y
7. Did patients enter the study at a similar point in the disease?	U	U	U	U	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	N	N	N	N	Y
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	U	Y	Y	U	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	N	Y	N	Y	Y
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	Y	Y	Y	Y	Y

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Table 4.5.9 IHE's quality appraisal checklist for cohort studies [20] (continued).

	Studies			
	Boltin et al. (2014)[57]	Chedid et al. (2014)[58]	Moraru et al. (2014)[59]	Gravina et al. (2015)[60]
Criterions				
Study objective				
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y
Study design				
2. Was the study conducted prospectively?	Y	N	Y	Y
3. Were the cases collected in more than one center?	N	N	Y	N
4. Were patients recruited consecutively?	Y	U	Y	Y
Study population				
5. Were the characteristics of the patients included in the study described?	Y	P	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Y	Y	Y	Y
7. Did patients enter the study at a similar point in the disease?	U	U	U	N
Intervention and cointervention				
8. Was the intervention of interest clearly described?	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	N	N	N	N
Outcome measures				
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y
Statistical analysis				
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y
Results and conclusions				
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	Y	Y	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y
18. Were the adverse events reported?	Y	Y	N	N
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y
Competing interests and sources of support				
20. Were both competing interests and sources of support for the study reported?	Y	Y	Y	Y

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Table 4.5.10 Meta-regression of eradication rate according to ITT analyses (studies included: 24*).

Covariate	Number of Studies	Coefficient	95% CI	p value
RCT	6	ref		
No RCT	18	*0.989*	*0.07 to 1.902*	*0.035*
Dosage of rifaximin	24	*0.002*	*0.0003 to 0.003*	*0.020*
Duration of treatment	24	-0.020	-0.084 to 0.043	0.512
GHBT	14	ref		
LHBT	10	-0.717	-1.535 to 0.099	0.081
Sample Size ≥ 50 patients	7	ref		
Sample Size < 50 patients	17	-0.093	-0.843 to 0.657	0.797
Studies performed in Italy	19	ref		
Studies not performed in Italy	5	-0.610	-1.808 to 0.587	0.299
Rifaximin as only treatment	21	ref		
Concomitant use of treatments affecting gut microbiota	3	*2.031*	*0.662 to 3.400*	*0.005*
Follow-up within 1 week after EOT	9	ref		
Follow-up between 2 and 4 weeks after EOT	13	-0.234	-1.064 to 0.596	0.562
Follow-up > 4 weeks after EOT	2	0.636	-0.856 to 2.130	0.383

*, being only two the studies where both breath tests were used [47, 56], these were not included in the regression analysis.
ref, reference; EOT, end of treatment.

Table 4.5.11 Sub-group analysis of eradication rate according to ITT analysis (studies included: 24*).

Variable	Number of Studies	Eradication Rate	95% CI
Randomization			
RCTs	6	65.8%	48.0 to 80.5
Not RCTs	18	71.4%	59.7 to 81.9
Daily dose of rifaximin and duration of treatment*			
600 mg/die for 7 days	1	16.7%	7.3 to 33.6
800 mg/die for 5 days	1	66.7%	30.0 to 90.3
800 mg/die for 7 days	2	68.5%	1.5 to 93.7
800 mg/die for 10 days	1	100%	93.2 to 100
800 mg/die for 28 days	1	50.0%	29.9 to 70.1
1200 mg/die for 5 days	1	66.7%	30.0 to 90.3
1200 mg/die for 7 days	10	62.9%	57.2 to 68.5
1200 mg/die for 10 days	9	72.9%	62.3 to 82.4
1200 mg/die for 14 days	1	87.9%	81.7 to 92.2
1200 mg/die for 28 days	1	34.3%	24.1 to 46.3
1600 mg/die for 7 days	1	80.0%	65.2 to 89.5
Type of H_2BT used			
GBT	14	70.8%	60.3 to 80.3
LHBT	10	68.8%	47.4 to 86.9
Number of patients enrolled in the study			
≥ 50 patients	7	73.4%	53.8 to 89.3
< 50 patients	17	67.7%	57.7 to 77.0
Country where the study was performed			
Italy	19	73.8%	63.0 to 83.3
Other Countries	5	55.8%	34.5 to 76.0
Concomitant use of treatments affecting gut microbiota			
Yes	3	95.1%	65.9 to 74.6
No	21	65.6%	56.1 to 74.6
Length of Follow-up			
Within 1 week	9	72.0%	51.1 to 89.1
Between 2 and 4 weeks	13	65.6%	55.1 to 75.3
> 4 weeks	2	88.2%	82.5 to 93.0

*, being only two the studies where both breath tests were used [47, 56], these were not included in the sub-group analysis.
*: number of studies is > 24 as several trials had ≥ 2 arms evaluating different doses and/or treatment durations.

Table 4.5.12 Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis.

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Corazza et al. (1988)[29]	GI	nr	Diarrhoea, bloating, weight loss, abdominal pain	Improvement of symptoms in 87.5% (95% CI: 52.9 to 97.8) of the eradicated patients Improvement of symptoms in 75.0% (95% CI: 30.1 to 95.4) of not eradicated patients
Biancone et al. (2000)[30]	GI (Patients with Crohn's Disease)	nr	CDAI	No change in CDAI
Di Stefano et al. (2000)[31]	GI	nr	GSS considering: abdominal pain, bloating, diarrhoea, borborygmi, lassitude, and anorexia evaluated and graded using a semi-quantitative scale (absent, mild, moderate, severe)	Only patients in the rifaximin group showed a significant reduction in symptom score for diarrhoea, borborygmi, and lassitude after therapy. In addition, the reduction in mean cumulative score of the patients treated with rifaximin was significantly higher ($p< 0.05$) than in those treated with chlortetracycline ($p=0.2$)
Cuoco et al. (2002)[32]	Extra GI (DM type I or II)	nr	GSS considering: bloating, diarrhoea, alternate alvine habits, using a four-point scale (absent, mild, moderate, severe)	Absence of symptoms in 72.2% (95% CI: 49.1 to 87.5) of the eradicated patients No change of symptoms in 66.7% (95% CI: 20.8 to 93.9) of not eradicated patients
Tursi et al. (2003)[33]	GI (Celiac Patients with persistence of gastrointestinal symptoms after gluten withdrawal)	nr	GSS considering: diarrhoea, slow gastric emptying, abdominal discomfort /abdominal pain with meteorism; symptoms were graded using the following scale: absence, slight symptoms, mild symptoms, severe symptoms	Absence of symptoms in 100% (95% CI: 72.2 to 100) of the eradicated patients
Lauritano et al. (2005)[34]	GI	nr	nr	nr
Tursi et al. (2005)[35]	GI (acute uncomplicated diverticulitis)	nr	Constipation, diarrhoea, abdominal pain, rectal bleeding, and mucus passage with the stools. Intensity of the symptoms quantified with a quantitative scale (0-10 according to increasing worsening of symptoms)	ne
Cazzato et al. (2006)[36]	GI (NERD)	nr	Heartburn relief	Absence of heartburn in 64.3% (95% CI: 38.8 to 83.7) of eradicated patients Absence of heartburn in 16.7% (95% CI: 31.0 to 56.4) of not eradicated patients
Cuoco et al. (2006)[37]	GI	Yes (diagnostic criteria not reported)	Abdominal discomfort, abdominal pain, meteorism, abdominal distension, irregular bowel movement or diarrhoea, evaluated using a four-level score scale (absence, mild to moderate, severe, very severe)	Statistically significant decrease of presence of symptoms ($p<0.05$) observed after treatment

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; CDAI, Crohn's Disease Activity Index; GSS, global symptom score; NERD, non-erosive reflux disease; VAS, visual analogue scale; ne, not possible to extract data. °, not possible to calculate 95% CI.

Table 4.5.13 Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
D'Incà et al. (2007)[38]	GI (UDD)	nr	Upper or lower abdominal pain, bloating, tenesmus, straining, stool frequency and characteristics, tenderness, dyspepsia recorded and graded according to the four-level score scale (no symptoms, mild, moderate, and severe); a GSS was calculated; a VAS was used to evaluate the overall treatment efficacy	GSS significantly reduced in the rifaximin group, while it remained practically unchanged after placebo administration ($p<0.005$); a similar result was observed when symptoms were evaluated according to the VAS
Esposito et al. (2007)[39]	GI	Yes (diagnostic criteria not reported)	Chronic diarrhoea, upper abdominal pain, lower abdominal pain, tenesmus, pain to palpation, abdominal bloating, flatulence, reduced body weight, nausea, steatorrhea, megaloblastic anaemia, stipsis, fever, others; GSS by means of VAS	Significantly reduction of symptom score from baseline in eradicated patients ($p = 0.004$)
Lauritano et al. (2007)[40]	Extra GI (Hypothyroidism)	nr	Abdominal discomfort/pain, bloating, flatulence, constipation, and diarrhoea assessed by a four-point scale (absence, mild, moderate, and severe symptoms)	A significant improvement in abdominal discomfort ($p<0.01$), bloating ($p<0.01$), and flatulence ($p<0.01$) was observed in the eradicated patients
Majewski et al. (2007)[41]	GI	Yes (Rome II Criteria)	Symptom assessment, and an overall score obtained by analysing frequency of stools, abdominal pain, bloating and gas before and after therapy	Improvement in overall symptom score was observed in 87.5% (95% CI: 52.9 to 97.8)
Majewski et al. (2007)[42]	GI	Yes§ (diagnostic criteria not reported)	Bloating, gas, abdominal pain, and bowel movements evaluated using a 4-point scale (non-disturbing or absent, mild, moderate; and severe)	After therapy, among patients with diarrhoea, 85.7% (95% CI: 60.1 to 96) of patients stated that they had improvement in their symptom score > 50%; among patients with either gas and bloating or constipation, 33% (95% CI: 9.7 to 70) had improvement between 50% and 75%, and 50% (95% CI: 18.8 to 81.2) an improvement between 25% and 50%. 16.7% (95% CI: 3.0 to 56.4) had no response to treatment
Resmini et al. (2007)[43]	Extra GI (Acromegaly)	nr	Chronic diarrhoea, abdominal pain either in the upper or lower part, meteorism, flatulence, nausea, tenesmus, weight loss, constipation, and fever	Disappearance of symptoms in 60%° of the treated patients
Scarpellini et al. (2007)[44]	GI	Yes§ (Rome II Criteria)	nr	nr

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; UDD, uncomplicated diverticular disease; VAS, visual analogue scale; ne, not possible to extract data.
§, part of the patients enrolled in the study presented IBS.

Table 4.5.14 Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Yang et al. (2008)[45]	GI	Yes (Rome I Criteria)	Percent improvement in IBS (number of participants with improvement of greater than 50%)	69% (95% CI: 58.5 to 77.9) of patients treated with rifaximin had a clinical response
Parodi et al. (2008)[46]	Extra GI (Scleroderma)	nr	Diarrhoea, upper and lower abdominal pain/discomfort, bloating, abdominal tenderness, nausea, emesis, dysuria, tenesmus, fever, general illness each carrying a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	Eradicated patients had a significant decrease in the median GSS score ($p<0.05$)
Parodi et al. (2008)[47]	Extra GI (Rosacea)	nr	Diarrhoea, upper and lower abdominal pain/discomfort, bloating, abdominal tenderness, nausea, emesis, dysuria, tenesmus, fever, general illness assessed using a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	Eradicated patients had a significant decrease in the median GSS score ($p=0.02$)
Lauritano et al. (2009)[48]	GI	Yes§ (Rome II Criteria)	nr	nr
Parodi et al. (2009)[49]	GI	Yes§ (Rome III Criteria)	Diarrhoea, upper and lower abdominal pain/discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea, constipation, and tenesmus assessed using a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	The median symptom severity score significantly decreased (> 50%) in eradicated patients as compared with the not eradicated ones ($p<0.001$)

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; VAS, visual analogue scale; ne, not possible to extract data; §, part of the patients enrolled in the study presented IBS.

Table 4.5.15 Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Peralta et al. (2009)[50]	GI	Yes (Rome II Criteria)	According to their intestinal habits, patients were divided into a constipation-variant, diarrhoea-variant or alternated alveus-variant; the severity of the alveus disturbances was scored according to a 5-point semi-quantitative scale (0 = none; 1 = minimum; 2 = mild; 3 = moderate; 4 = severe)	In eradicated patients, a statistically significant reduction of the symptomatological score was achieved ($p = 0.003$); on the contrary, in non-eradicated patients no change in the symptomatological score was observed (p = not significant)
Furnari et al. (2010)[51]	GI	nr	Diarrhoea, upper and lower abdominal pain / discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea, constipation and tenesmus assessed using a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	Clinical improvement (> 50% GSS) was observed in 86.9% (95% CI: 67.9 to 95.5) and 91.1% (95% CI: 77.0 to 97.0) of eradicated cases in rifaximin and rifaximin-plus-partially hydrolysed guar gum group, respectively ($p = 0.677$); among patients who did not obtain eradication, clinical improvement was observed in 7.1% (95% CI: 1.3 to 31.5) and 16.6% (95% CI: 3 to 56.46) respectively ($P = 0.521$)
Lauritano et al. (2010)[52]	GI	nr	nr	nr
Lombardo et al. (2010)[53]	GI	Yes§ (Rome III Criteria)	Pain severity, pain duration, pain frequency, bloating, and constipation/diarrhoea assessed using a 4-point scale (absence, mild, moderate, and severe)	In eradicated patients, bloating was improved or absent in 90%*, diarrhoea in 94%*, and abdominal pain in 92%* of the cases; in non-eradicated patients, bloating was improved or absent in 30%*, diarrhoea in 35%*, and abdominal pain in 20%* of the cases
Cerda et al. (2012)[54]	GI	Yes (Rome III Criteria)	ne	ne
Meyrat et al. (2012)[55]	GI	Yes (Rome III Criteria)	Bloating, diarrhoea, flatulence, abdominal pain and overall well-being. The symptom severity as well as changes in overall well-being assessed on a 11-point Likert scale, where 0 corresponded to absence of symptoms or no reduction in overall well-being and 10 corresponded to most severe symptoms or severe reduction in overall well-being	2 and 12 weeks after completion of therapy a significant reduction in all the assessed items was observed ($p \leq 0.015$)
Fasano et al. (2013)[56]	Extra GI (Parkinson's disease)	ns	ne	ne

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; VAS, visual analogue scale; ne, not possible to extract data.
§, part of the patients enrolled in the study presented IBS.

Table 4.5.16 Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Boltin et al. (2014)[57]	GI	Excluded IBS patients according to Rome III criteria	Bloating, flatulence	No patients reported any degree of resolution for either bloating or flatulence
Chedid et al. (2014)[58]	GI	Yes[§] (Rome III Criteria)	nr	nr
Moraru et al. (2014)[59]	GI	Yes[§] (Rome III Criteria)	Severity (using a Likert scale) and type of IBS symptoms	Among IBS patients treated with rifaximin 46.7% (95% CI. 37.4 to 56.2) had a complete response, 31.4% (95% CI. 23.3 to 40.8) had a partial response, and 21.9% (95% CI. 15.1 to 30.7) had no response
Gravina et al. (2015)[60]	Extra GI (Rosacea)	ns	Upper GI symptoms using SF-LDQ + bloating, flatulence, abdominal pain, diarrhoea and constipation using a questionnaire assessing frequency and severity of each symptom during the last two months	nr

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; VAS, visual analogue scale; ne, not possible to extract data; SF-LDQ, Short-Form Leeds Dyspepsia Questionnaire.
[§], part of the patients enrolled in the study presented IBS.

Table 4.5.17 Meta-regression of adverse events rates*.

Covariate	Number of Studies	Coefficient	95% CI	p value
RCT	4	ref		
No RCT	13	*-1.577*	*-2.484 to -0.670*	*0.002*
Dosage of rifaximin	17	0.0005	-0.0009 to 0.0018	0.446
Duration of treatment	17	0.026	-0.059 to 0.112	0.520
Sample Size ≥ 50 patients	5	ref		
Sample Size < 50 patients	12	0.514	-0.268 to 1.296	0.180
Studies performed in Italy	12	ref		
Studies not performed in Italy	5	0.771	-0.700 to 2.243	0.279

*: concomitant use of fibre, mesalazine, pre or probiotics was not evaluated as all the studies included in the model used only rifaximin.
ref, reference.

Table 4.5.18 Sub-group analysis of adverse event rate*.

Variable	Number of Studies	Adverse Event Rate	95% CI
Randomization			
RCTs	4	13.1%	9.4 to 18.1
Not RCTs	13	4.6%	3.0 to 6.9
Daily dose of rifaximin and duration of treatment°			
600 mg/die for 7 days	1	10%	3.3 to 26.8
800 mg/die for 7 days	1	13.3%	5.1 to 30.6
800 mg/die for 14 days	1	4.7%	1.5 to 10.7
800 mg/die for 28 days	2	3.6%	0.5 to 21.7
1200 mg/die for 7 days	8	8.8%	4.8 to 15.6
1200 mg/die for 10 days	4	3.5%	1.0 to 11.4
1200 mg/die for 14 days	1	2.0%	0.7 to 6.1
1200 mg/die for 28 days	1	9.0%	4.1 to 18.5
1600 mg/die for 7 days	1	15.0%	6.9 to 29.6
Number of patients enrolled in the study			
≥ 50 patients	5	5.1%	2.7 to 9.5
< 50 patients	12	10.9%	7.7 to 15.3
Country where the study was performed			
Italy	12	8.0%	5.1 to 12.3
Other Countries	5	6.1%	3.5 to 10.3

*: concomitant use of fibre, mesalazine, pre or probiotics was not evaluated as all the studies included in the model used only rifaximin.
°: number of studies is > 17 as several trials had ≥ 2 arms evaluating different doses and/or treatment durations.

Figure 4.5.1 Funnel plot of SIBO eradication rate according to ITT analysis.

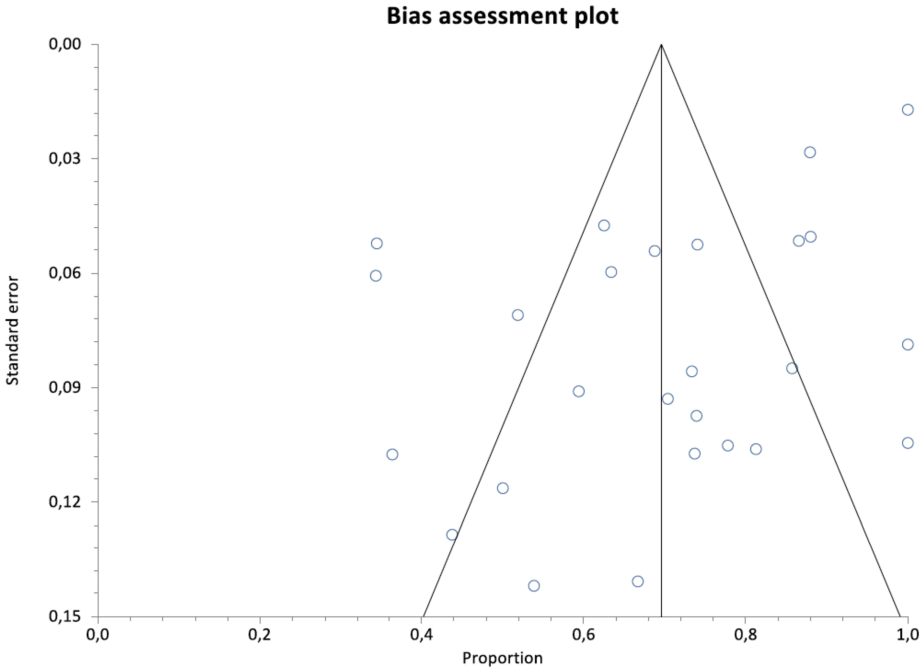
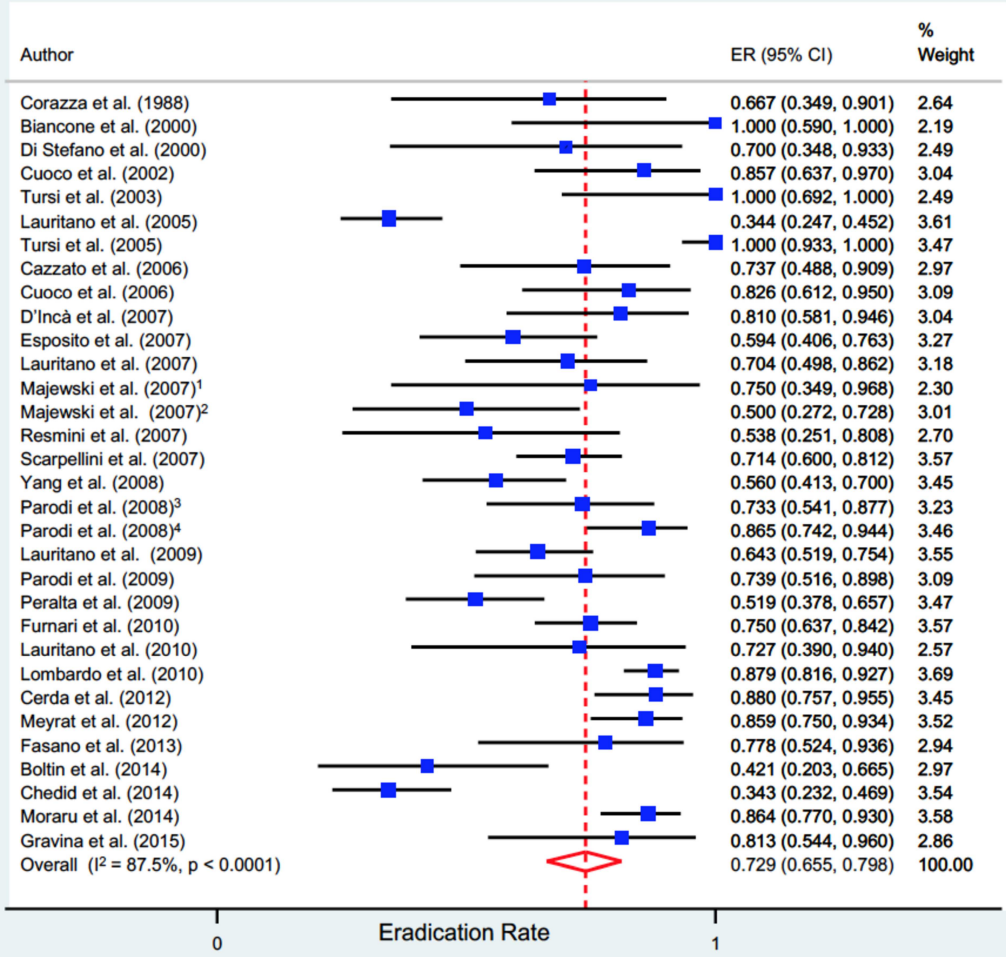


Figure 4.5.2 Forest plot of SIBO eradication rate according to PP analysis.



ER, eradication rate.
1, ref; 41; 2, ref. 42; 3 , ref; 46; 4 , ref. 47.

Figure 4.5.3 Funnel plot of SIBO eradication rate according to PP analysis.

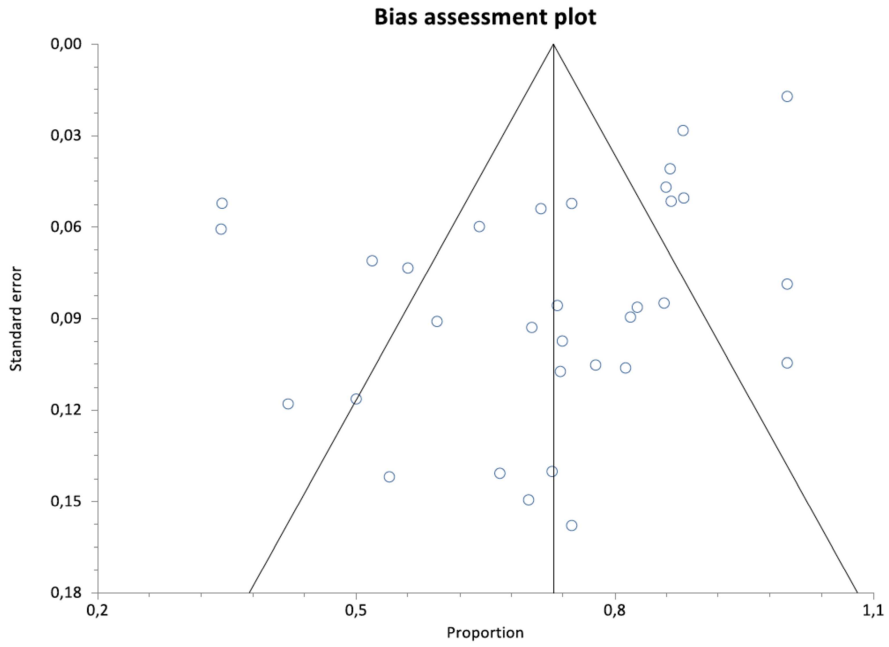


Figure 4.5.4 Funnel plot of SIBO eradication rate in IBS according to ITT analysis.

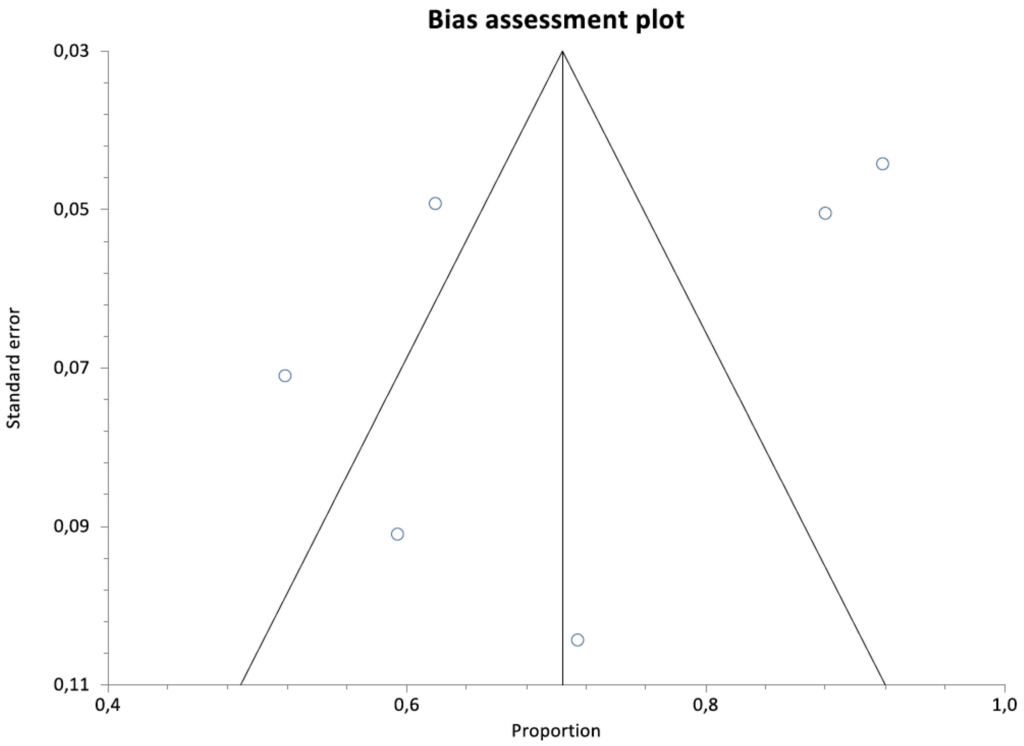
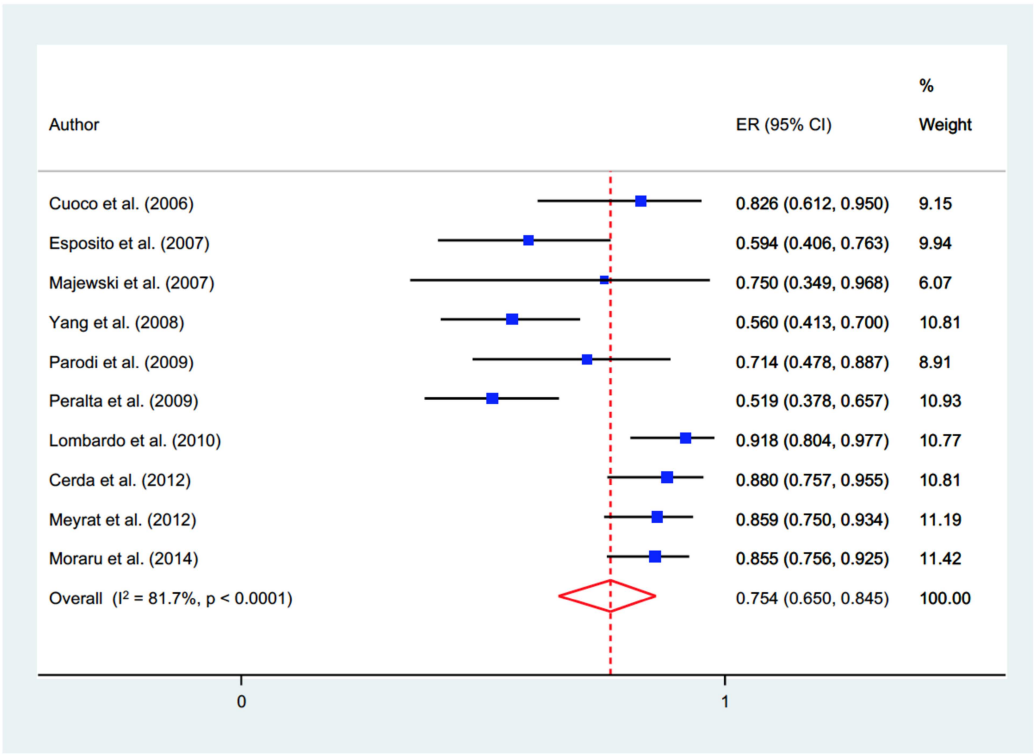


Figure 4.5.5 Forest plot of SIBO eradication rate in IBS according to PP analysis.



ER, eradication rate.

Figure 4.5.6 Funnel plot of SIBO eradication rate in IBS according to PP analysis.

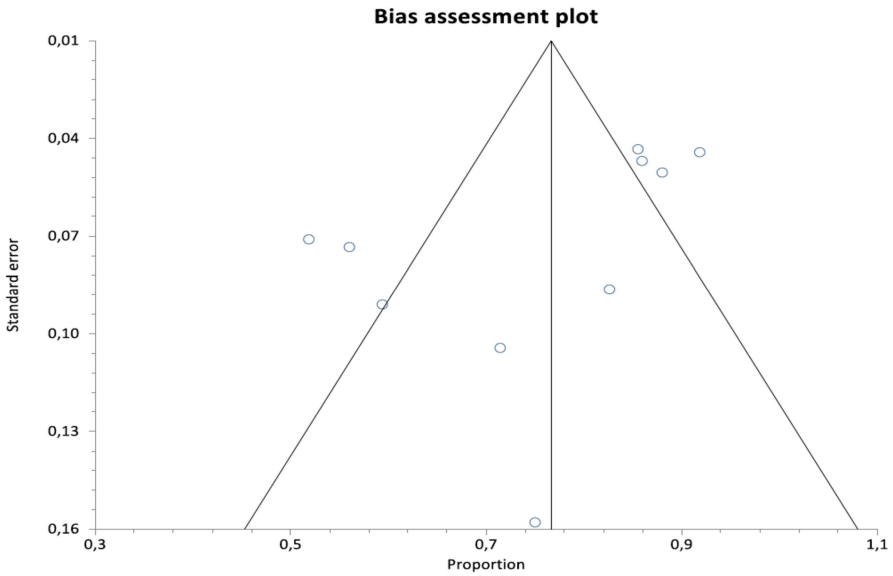
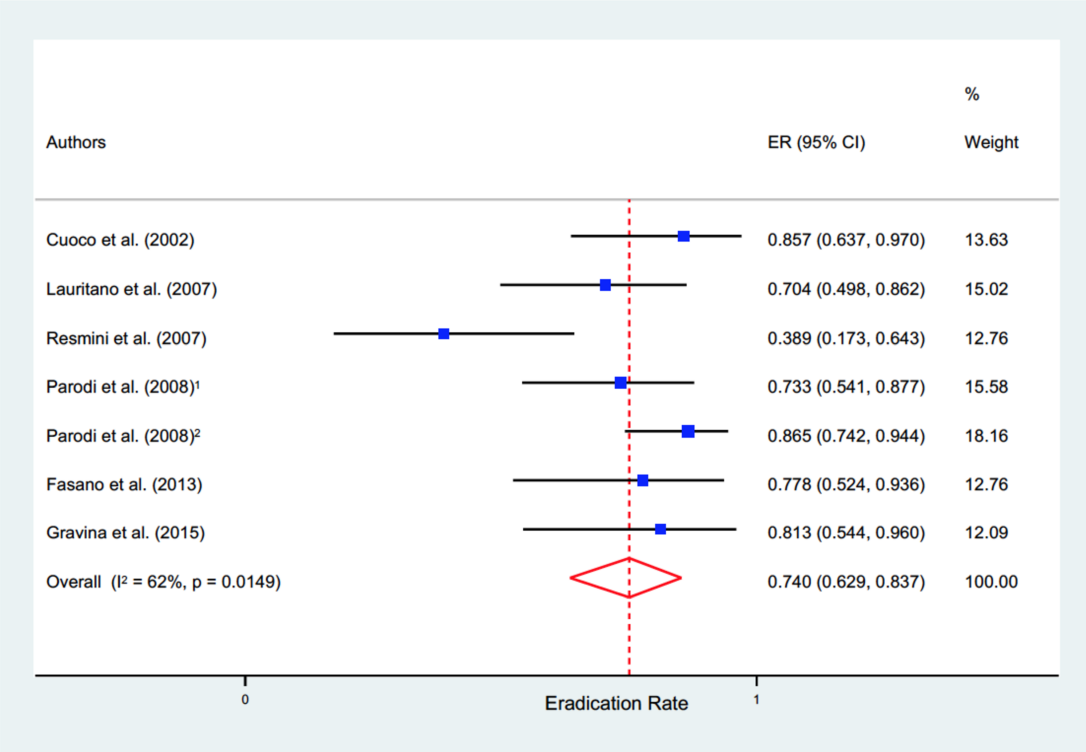


Figure 4.5.7 Forest plot of SIBO eradication rate in Extra GI settings according to ITT analysis.



ER, eradication rate.
1, ref; 46; 2, ref. 47.

Figure 4.5.8 Funnel plot of SIBO eradication rate in Extra GI settings according to ITT analysis.

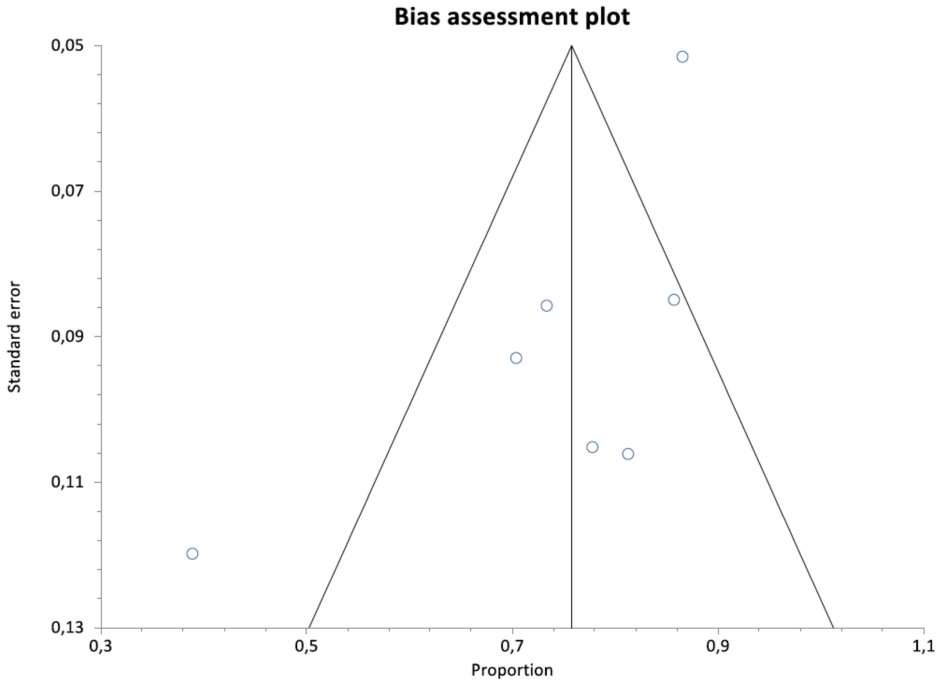
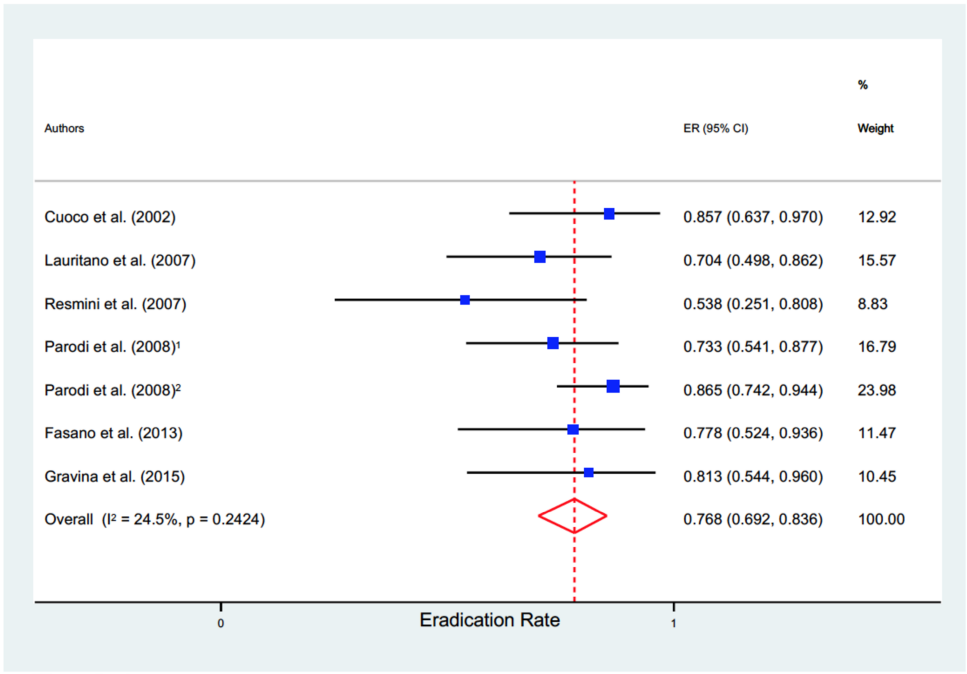


Figure 4.5.9 Forest plot of SIBO eradication rate in Extra GI settings according to PP analysis.



ER, eradication rate.
1, ref; 46; 2, ref. 47.

Figure 4.5.10 Funnel plot of SIBO eradication rate in Extra GI settings according to PP analysis.

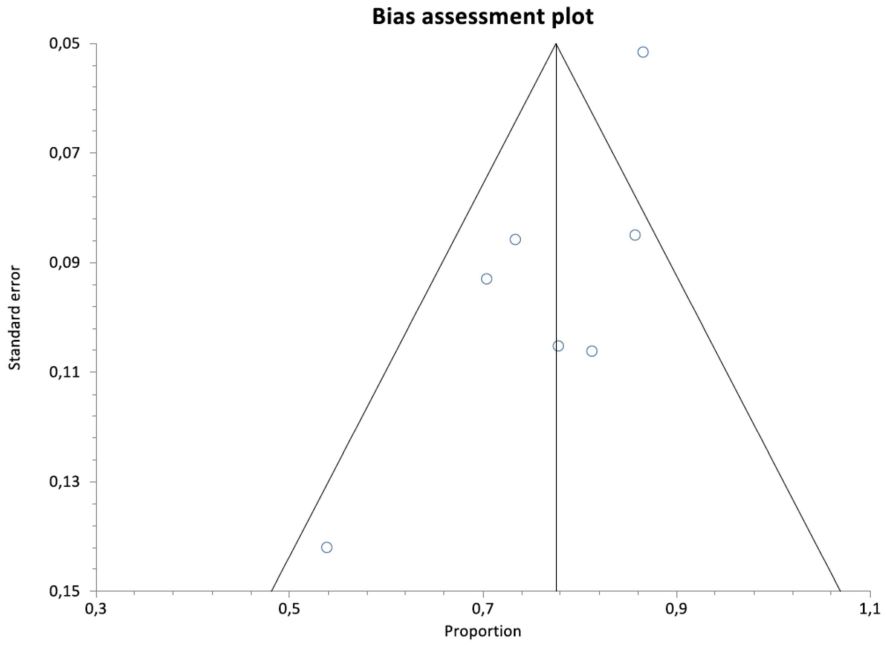
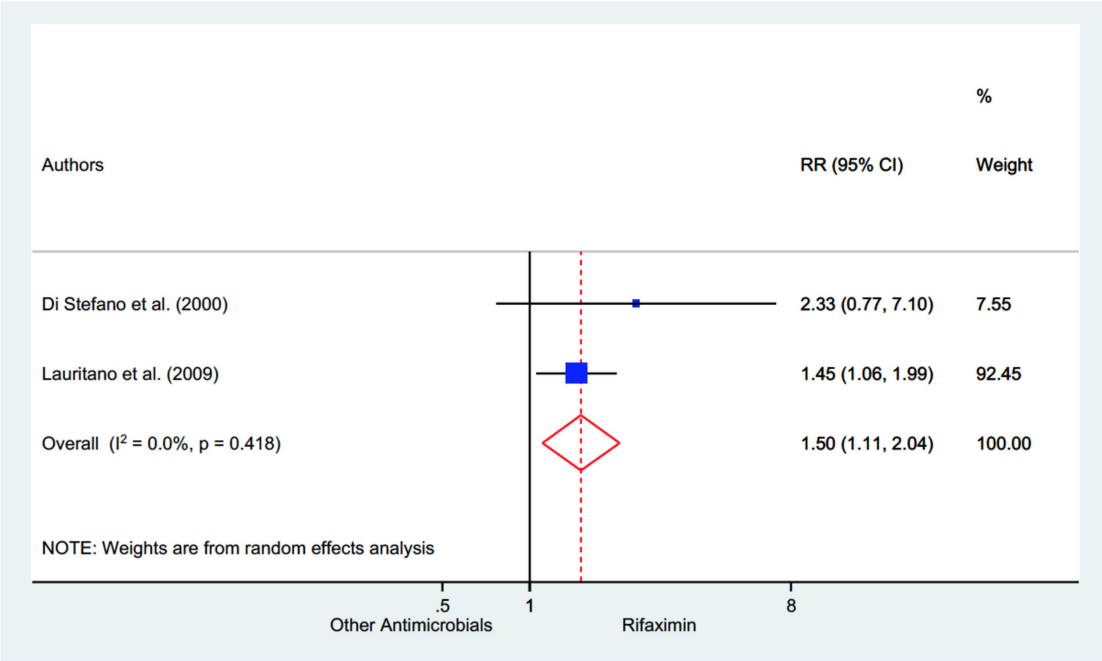
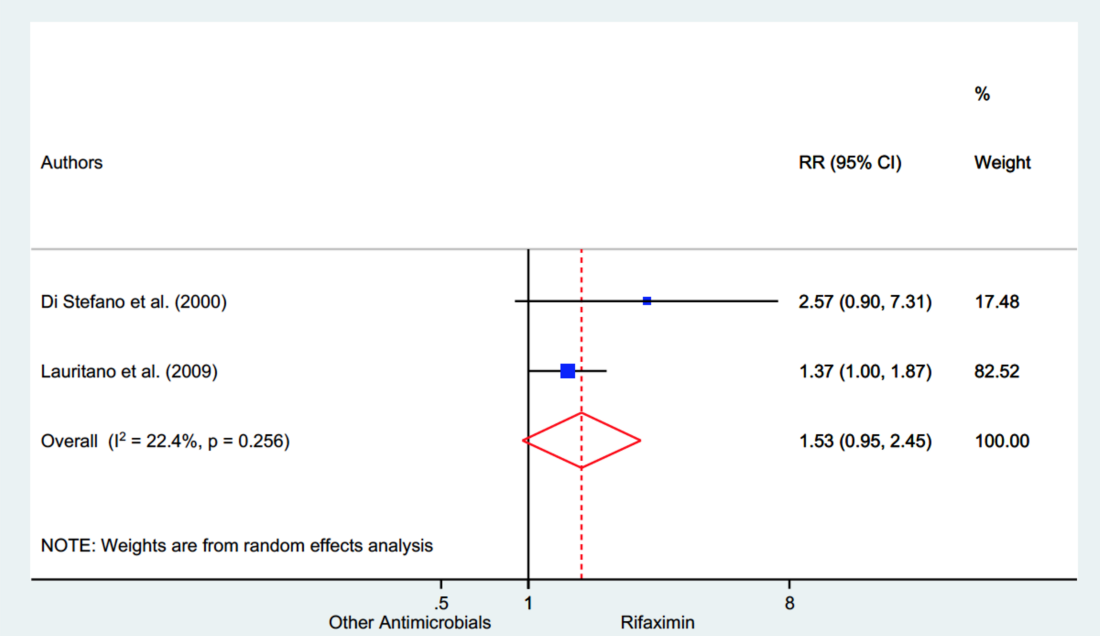


Figure 4.5.11 Forest Plot: rifaximin vs. other antimicrobials in RCTs according to ITT analysis.



RR, relative risk.

Figure 4.5.12 Forest plot: rifaximin vs. other antimicrobials in RCTs according to PP analysis.



RR, relative risk.

Figure 4.5.13 Symptom evaluation before and after treatment with rifaximin.

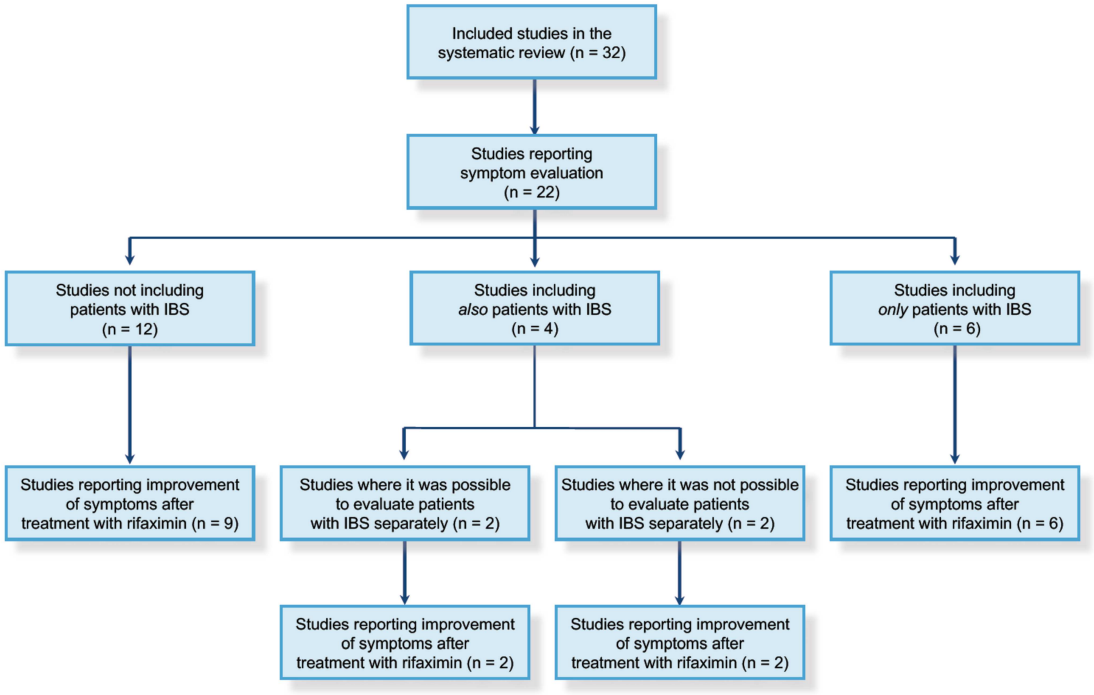
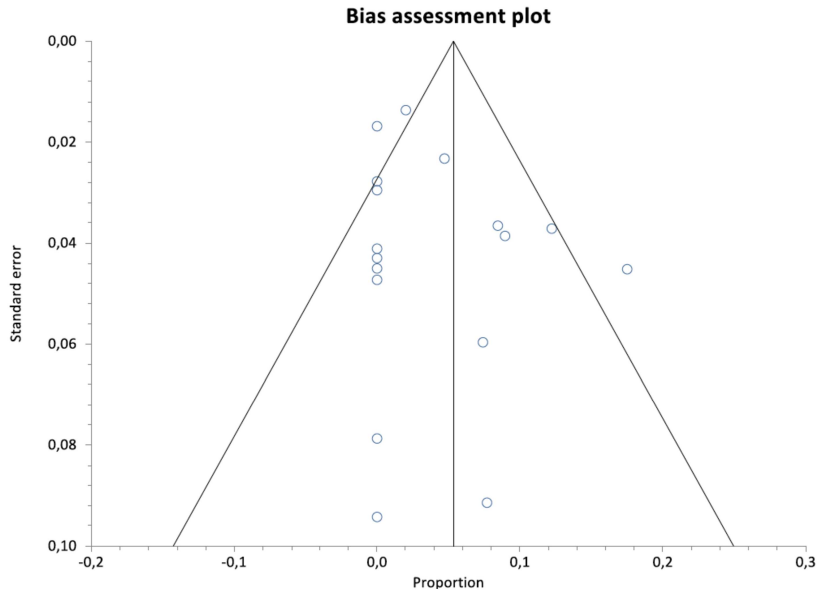


Figure 4.5.14 Funnel plot of adverse events in patients taking rifaximin alone for SIBO eradication.



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5 Effective and Safe Proton Pump Inhibitor Therapy in Acid-related Diseases

5.1 Introduction

The introduction of proton pump inhibitors (PPIs) into clinical practice has revolutionized the management of acid-related diseases. Pharmacological acid suppression has been so successful in healing peptic ulcers (PU) and managing patients with gastro-esophageal reflux disease (GERD) that elective surgery for ulcer disease has been virtually abolished and anti-reflux operations are today performed only in selected patients. Along the same lines, the incidence of non-steroidal anti-inflammatory drug (NSAID) associated gastropathy has largely been reduced, despite the increased use of these medications in the aging population [1].

Despite the fact that PPIs are far from being the ideal antisecretory drugs [2], and new longer-acting compounds with extended acid suppression are being developed [3-5], they are - no doubt - the most effective currently available medications and are widely prescribed in all age populations. Health care providers are increasingly prescribing PPIs for prolonged, sometimes lifetime, use and there is growing concern for potential adverse effects resulting from such long-term therapy [6, 7]. Soon after the introduction of omeprazole, the first PPI, into the market, Jean Paul Galmiche, a leading French gastroenterologist, wrote a thoughtful article [8] anticipating that the unprecedented clinical efficacy of these drugs would have lead (patients and physicians alike) to addiction. And indeed, this is the case. Once on a PPI, the majority of patients stay on long-term PPIs, often indefinitely [9], especially in the elderly [10].

Studies in primary care and emergency settings suggest that PPIs are frequently prescribed for inappropriate indications or for indications where their use offers little benefit [11]. Patients admitted to hospital frequently are started on PPIs, often inappropriately [12], and these medications are continued, following discharge, by primary care physicians. Indeed, inadequate recommendations for PPIs in discharge letters are

quite frequent [13]. This prescription habit may lead to a continuation of PPI therapy in primary care, thereby unnecessarily increasing polypharmacy and the risk of adverse events as well as burdening the public health budget. In this connection, an Italian study [14] found that the persistence rate of PPI therapy is fairly high, after both appropriate and inappropriate prescriptions (62% and 71%, respectively). The GPs' attitude to continuing or discontinuing PPIs depends on their level of knowledge and their perceptions of hospital physicians' competence and the threshold to prescribing in hospitals [15].

The introduction of generic PPIs into the market has been followed by an increasing rate of PPI prescribing related to chronic treatments, unlicensed indications and therapeutic substitutions [16]. Furthermore, since PPIs are now available over-the-counter [17], patients can have free access to them and for long periods of time, without seeking medical attention [18, 19]. Counselling is therefore important to ensure that patients understand that failure of symptoms to resolve or a rapid symptom relapse while taking a PPI is an indication to consult a physician. Furthermore, concerns about potential masking of more serious pathology, such as malignancy, should not be overlooked [19].

Inappropriate PPI use is a matter of great concern, especially in the elderly, who are often affected by multiple comorbidities, are taking multiple medications, and hence are at an increased risk of long-term PPI-related adverse outcomes and drug-to-drug interactions (DDIs). There is indeed a strong relationship between the number of administered drugs and potential, clinically-relevant DDIs [20], particularly in older adults [21]. As a consequence, the number of yearly papers, reporting PPI-related adverse events and/or PPI-drug interactions, has steadily increased over the past decade [22-25].

Together with inappropriate use, underuse is also of concern. For instance, despite all guidelines support the use of gastroprotection with PPIs in at-risk patients treated with NSAIDs [26-28], low prescription rates of gastro-protective medications have been reported, even though these rates were increased progressively (*for review see* [28]). In Italy, three studies [29-31] reported a substantial misuse of gastroprotection in primary

care. In particular, an underuse rate of 25–30% or an overuse (young patients without any concomitant risk factor) as high as 57.5% were observed. In addition, half PPI-dose or ineffective H_2-receptor antagonist (H_2RA) treatment were prescribed in another 10% of subjects [30].

According to the data provided by the Organization for Economic Cooperation and Development (OECD [32]) PPI use is widespread and currently increasing, especially in some European Countries. Prescription rates have risen substantially, not only as a consequence of the replacement of H_2RA but also because of an expansion in the overall market. PPI utilization does not appear to be commensurate with prevalence of acid-related disease (particularly with GERD and NSAID-gastropathy) nor with prescribing guidelines, thus leading to significant increment costs to both patients and the National Health System (NHS). Inappropriate prescribing is therefore high and costly. In a US teaching hospital, the estimated cost of inpatient and outpatient inappropriate use of PPIs was $12,272 and $59,272, respectively [33]. This trend is being observed as well in almost all the industrialized Countries and Italy makes no exception.

Taking all the above considerations into account, the Italian Society of Pharmacology (SIF), the Italian Association of Hospital Gastroenterologists (AIGO) and the Italian Federation of General Practitioners (FIMMG) considered it wise to review the current literature on PPI use and to prepare a position paper addressing benefits and potential risks of acid suppression with the aims of providing evidence-based guidelines for appropriate use of these medications.

5.2 Methods

The three scientific societies (SIF, AIGO, FIMMG), promoters of the endeavour, identified the experts amongst their members, in order to set-up the Scientific Committee, who defined the methodology to follow in the preparation of the position paper.

The methodology to process the recommendations consisted of four subsequent steps. In a meeting, held in Rome at the beginning of 2015, the Scientific Committee identified the following 13 clinically relevant areas, which leave Primary Care Physicians as well as gastroenterologists uncertain about how to prescribe these drugs in patients with acid-related diseases and where PPI-misuse was found to be common:

1. GERD
2. Eosinophilic Esophagitis
3. *H. pylori* eradication and peptic ulcer disease
4. Zollinger-Ellison Syndrome
5. Stress Ulcer prophylaxis
6. Dyspepsia
7. NSAID-associated GI Symptoms and Lesions
8. Corticosteroid use
9. Anti-Platelet or Anticoagulant Therapy
10. Peptic Ulcer Bleeding
11. Patients with Cancer
12. Cirrhosis
13. Pancreatic Disease

Since PPI therapy is often used long-term, the safety concerns dealing with such a therapy were also addressed to put appropriateness in a benefit-to-risk perspective.

Each selected topic was assigned to a given expert, who carried out an independent a systematic search of the relevant literature using Medline/PubMed, Embase and the Cochrane databases. Search outputs were distilled, paying more attention to systematic

reviews and meta-analyses (where available), representing the best evidence.

For each topic, a draft was prepared and circulated amongst all the members of the Scientific Committee. Each expert then provided her/his input to the writing, suggesting changes, inclusion of new material and/or additional relevant references. Following preparation of the revised draft, each topic was addressed to the Core Writing Group, who prepared the first draft of the full manuscript, which was examined in Bologna on June 2015. During the meeting, each single topic was thoroughly discussed and each statement concerning the summary of current evidence refined with regard to both content and wording.

The Core Writing Group then incorporated all the suggestions raised during the Bologna meeting and prepared the final draft. In doing so, an updated literature search was performed and the more recent evidence included. This revised document was then sent to Italian and International authorities for review. Any changes resulting from comments received by the external experts were made on the basis of scientific and editorial merit in order to produce the final version of the position paper.

5.3 Results

5.3.1 Proton Pump Inhibitors for GERD

Summary of the current evidence: *PPIs represent the mainstay of medical treatment of esophageal manifestations of GERD; however, their benefit (if any) in extra-digestive GERD are still uncertain. Eight-week therapy with standard (once daily) dose PPIs can achieve healing of reflux esophagitis and get symptom relief in more than 80% of patients with typical symptoms. When a functional investigation is added to a negative endoscopy in making the diagnosis, PPI efficacy in GERD and NERD appears comparable. Being a chronic, relapsing disease, GERD (as well as NERD) requires long-term PPI treatment, which can be continuous, intermittent or on-demand. Profound and individually tailored maximal acid suppression is needed in patients with Barrett's esophagus not only to control GER but also in the hope to achieve a chemopreventive effect against neoplastic transformation.*

Gastro-esophageal reflux (i.e. the reflux of gastric contents into the esophagus, GER) is a physiological phenomenon, occurring in everybody, especially after large and fat meals. In physiological conditions, efficient esophageal clearing mechanisms return most of the refluxed material to the stomach and symptoms do not occur [34]. However, when the reflux of gastric contents is large or aggressive enough, it causes troublesome symptoms and/or complications and adversely affects health-related quality of life, giving rise to GER disease (GERD) [35]. The Montreal consensus sub-classified the disease into esophageal and extra-esophageal syndromes, with established or proposed associations with GER [36]. Up to two-third of patients with esophageal symptoms have a macroscopically normal mucosa at endoscopy. Such patients are usually considered to have non-erosive reflux disease (NERD) [37, 38].

GERD is primarily a motor disorder and its pathogenesis is multifactorial. The main motility abnormalities include an impaired function of the lower esophageal sphincter (LES), an abnormal esophageal clearance and a delayed gastric emptying in up to 40% of cases. The presence of hiatal hernia favours reflux, but this association is not mandatory. The ultimate consequence of the above motor abnormalities is the presence of acid in the wrong place (i.e. in contact with the esophageal mucosa) [39]. In addition, the amount of reflux increases markedly after meals in both healthy subjects and in GERD patients, an event almost exclusively due to the increase of transient (inappropriate) LES relaxations by food-induced gastric accommodation. Despite the buffering content of food, the pH of the material refluxed into the distal esophagus is very acid due to the presence of an "acid pocket", which occurs in both healthy subjects and GERD patients. It represents an area of unbuffered gastric acid that accumulates in the proximal stomach after meals and serves as a reservoir for acid reflux [40]. The abnormal esophageal exposure to acid, on the other hand, is not secondary to gastric acid hypersecretion, which has been documented in only in a small subset of GERD patients [39]. All the above pathophysiological mechanisms are exaggerated in obese subjects [41, 42].

Since, currently, effective drugs capable of controlling the esophageal motor abnormalities are lacking, the mainstay of medical treatment for GERD are antisecretory drugs, which act indirectly by reducing the amount and concentration of gastric secretion available for reflux, thus lessening the aggressive power of the refluxed material [43]. PPIs also reduce the size of the acid pocket and increase the pH (from 1 to 4) of its content [40]. The clinical efficacy of these drugs has been clearly shown in many studies and the superiority of PPIs over H_2RAs has been established beyond doubt [44]. The greater pharmacodynamic effect of PPIs depends on their ability to block the final step in the production of acid, regardless the secretory stimulus. Moreover, PPIs are relatively more effective during the daytime than the night-time and this leads to a better control of post-prandial reflux events [44].

Eight-week therapy with standard (once daily) dose PPIs can achieve healing of reflux esophagitis in more than 80% of patients [45], a rate depending on the severity of mucosal lesions [46, 47]. This healing rate can be further improved by doubling the PPI dose (NNT=25) [45]. Meta-analyses have shown that - when compared to omeprazole, lansoprazole and pantoprazole - esomeprazole achieves the highest healing rates of reflux esophagitis in the short-term [46, 48, 49]. The more favourable clinical benefit of esomeprazole appears negligible in less severe esophagitis (A & B according to the Los Angeles classification [50, 51]), but it might be important in more severe disease [48]. Vonoprazan, a member of the new generation *reversible* PPIs (called potassium-competitive acid blockers, P-CABs), is able to achieve higher intragastric pH and controlling effectively both daytime and night-time acid secretion [5], As a consequence, it proved to be capable of healing almost 100% of severe (C & D) esophagitis [52], a benefit also maintained during the remission phase [53].

It is worth mentioning that currently available PPI regimens do not provide the same control of intragastric pH, evaluated both in terms of mean pH over the 24 hours and % time spent at pH>4. This has been repeatedly demonstrated in patients with GERD [54-56] or taking NSAIDs [57]. A large meta-analysis [58], including 57 studies measuring intragastric pH after different PPI regimens, found that the relative potencies of the five compounds, compared to omeprazole, were 0.23, 0.90, 1.60, and 1.82 for pantoprazole, lansoprazole, esomeprazole, and rabeprazole, respectively. This lack of pharmacodynamic equivalence should be taken into account when switching from a given PPI to another.

PPIs are effective in obtaining symptom relief in both erosive and non-erosive disease [59]. Their efficacy for the relief of regurgitation is however modest, and considerably lower than that achieved for heartburn [60]. The myth that PPIs are less effective in NERD has recently been dispelled by a meta-analysis [61], showing that – when a functional investigation (pH-metry or pH-impedance-recording) is added to a negative endoscopy

to objectively confirm this condition - the estimated complete symptom response rate after PPI therapy is comparable to that observed in patients with erosive disease.

NERD is however an umbrella term, including at least 4 different patient subgroups [38], of which only those where acid is implicated in symptom generation (i.e. true NERD and patients with acid hypersensitive esophagus) are clearly responsive to PPIs [62]. This is not the case of patients who are hypersensitive to nonacidic reflux or those with functional heartburn. According to Rome IV criteria [63], both acid hypersensitive esophagus (now called *reflux hypersensitivity*) and functional heartburn are functional GI disorders, which should be no longer included in GERD. The lack of abnormal acid exposure and symptom-reflux association makes patients with functional heartburn not responsive to PPIs. This subgroup of subjects may benefit of visceral analgesics (e.g. antidepressants) [64].

Although not as frequent as previously suggested, PPI-refractory heartburn, occurring more commonly in NERD than in erosive disease, does exist however. Some 20% (range 15-27%) of correctly diagnosed and *appropriately* treated patients do not respond to PPI therapy at standard doses [65]. To ascertain whether they are "truly" PPI-resistant, compliance and adherence to treatment should be checked. Indeed, PPIs are often taken inappropriately, with only 27% of GERD patients dosing their PPI correctly and only 12% dosing it optimally in a USA survey [66]. Although a standard PPI dose can occasionally control symptoms, nocturnal intragastric acidity often remains elevated (with Nocturnal Acid Breakthrough, NAB) in these patients. A split regimen (either standard or double dose) of PPIs b.i.d. (before breakfast and before evening meal) provides superior acid control. In patients with persistent nocturnal symptoms, the addition of an H_2RA at bedtime may be indicated to control NAB and associated esophageal acidification [3, 62, 67, 68], despite the likely development of tolerance to H_2RA [69]. The majority of patients, however, reported persistent improvement in GERD symptoms from night-time H_2RA use[67]. To reduce the development of tolerance, on

demand or cyclic dosing may be preferable, but this approach has not been specifically studied.

GERD and NERD are chronic, relapsing diseases. Six months after cessation of treatment, symptomatic relapse is rapid and frequent (i.e. in 90 % of endoscopy-positive and 75 % of endoscopy-negative patients [70]). PPIs, both at a full and half dose, are able to maintain patients in remission, with a superior efficacy of the full dose (NNT=9.1) [71]. Esomeprazole 20 mg is the only step-down dose PPI able to maintain in symptomatic remission a significantly higher proportion of GERD patients compared to lansoprazole 15 mg [49, 72] or pantoprazole 20 mg [49].

Since PPIs do not correct the underlying pathophysiological motor abnormalities responsible for GERD, a continuous treatment is required to maintain all patients in remission. In the LOTUS trial [73], comparing long-term esomeprazole therapy with anti-reflux surgery (ARS), the estimated remission rate at 5 years was 92%, higher than that (57%) reported with omeprazole in the SOPRAN study [74]. However, while the PPI dose in the SOPRAN trial was fixed, in the LOTUS investigation, patients whose reflux symptoms were not adequately controlled by a standard maintenance regimen (i.e., esomeprazole, 20 mg/die) were allowed to increase the dosage to 40 mg once daily and then to 20 mg twice daily. This dose titration may have contributed to the improved remission rate and suggests that long-term maintenance therapy should be individualized. Indeed the number and severity of relapses are highly variable amongst patients. Infrequent reflux symptoms are less likely to be chronic and may respond to different management strategies. There are basically three different long-term approaches for GERD treatment with PPIs: continuous (i.e. every day), intermittent (i.e. cycles of daily PPI administration) or *on-demand* (i.e. symptom-driven) therapy, each selected on the basis of patients' clinical characteristics [75].

One third of patients, submitted to fundoplication, is reported to take acid-lowering compounds (mostly PPIs) after anti-reflux surgery, but only few studies have specified

whether drug use was on a regular or occasional basis [76]. A meta-analysis of RCTs [77] found that – after anti-reflux surgery - 14% of patients still require antisecretory drugs. This figure increases with the duration of follow-up and up to one third of patients required antisecretory drugs after 10 years. The data from non-randomized studies [78], which are higher than estimation provided by randomized studies (i.e. 20% of patients under acid suppression), are probably more representative of the current clinical practice.

Although medication use is often considered as an outcome measure for successful antireflux surgery, some studies have shown that antisecretory drug use does not correlate with true recurrent reflux in most patients [76] and does not necessarily indicate a failure of the procedure. A significant proportion of patients taking medications after operation are using them to relieve *non-reflux symptoms* and only one third of patients displays an abnormal esophageal exposure to acid after surgery [76]. Therefore, many patients take PPIs despite the lack of objective evidence of GERD on esophageal testing. The causes of persistent symptoms after surgery remain unclear. Non-GERD symptoms might be due to increased esophageal sensitivity while other symptoms (like bloating, early satiety and nausea) may be unmasked when reflux symptoms improve [79-81]. A careful selection of patients and thorough follow-up is needed to avoid unnecessary acid suppression in post-surgical patients.

Before embarking on long-term treatment, an attempt to stop acid suppression must always be considered. Of the various interventions (patient's education, life-style modifications, abrupt withdrawal and tapering), tapering is the more effective discontinuation strategy [82]. Abrupt withdrawal might be followed by rebound acid hypersecretion and exacerbation of symptoms [83]. Weight loss appears to be another strategy in obese/overweight patients. Indeed, in one study, up to 54% of subjects compliant to a hypocaloric diet were able to stop PPI therapy, with an additional 32% being able to halve the dose [84]. All the above attempts should be considered also in patients who are already on long-term acid suppression.

Continuous maintenance therapy is indicated in patients with Barrett's esophagus of any mucosal length, owing to the potential chemopreventive activity of PPIs against neoplastic transformation, a property advocated by the ACG [85] and AGA [86] but denied by the BSG guidelines [87]. Indeed, a recent meta-analysis of observational studies showed that PPI use is associated with a 71% reduction in risk of esophageal adenocarcinoma and/or high-grade dysplasia in this patient population (adjusted OR 0.29) [88]. Despite a contrary opinion of the AGA [86], current evidence suggests that standard PPI therapy is unable to normalize esophageal exposure to acid in the vast majority of patients with Barrett's esophagus. Profound and individually tailored maximal acid suppression is needed not only to control GER but also in the hope to achieve a better chemopreventive effect [89].

In all those patients with GERD, requiring long-term PPI therapy, *Helicobacter pylori* should be sought and – if present - eradicated particularly in young patients. This approach, recommended by international guidelines [90, 91], is needed to prevent the development of atrophic gastritis or worsening of any pre-existing one, with potential for neoplastic transformation [92]. However, in accordance with the Food and Drug Administration (FDA), ACG guidelines [93] do not recommend *routine* screening for or treatment of *H. pylori* infection in GERD patients (strong recommendation, low level of evidence).

Conversely from typical symptoms, the efficacy of PPIs on extra-esophageal manifestations of GERD is uncertain. This uncertainty could result, at least in part, from the available studies, which are not homogenous, with differences in patient selection, end-point considered, drug used and regimen adopted. In addition, since extra-digestive symptoms may need higher PPI dose and clinical improvement may take a longer time to occur, only properly designed trials would be able to unravel a clinical response. Unfortunately, however, this has not always been the case.

The efficacy of PPIs in non-cardiac chest pain (NCCP) and extra-digestive GERD is disappointing. In these clinical conditions, PPIs are usually given twice daily and for extended periods (i.e. 3 or more months). However, evidence is often lacking and, where available, not strong enough to allow clear recommendations to be made.

GERD being the most common and best-studied cause of NCCP, acid suppression is the initial pharmacological approach in this patient population. A systematic review showed that patients with endoscopic or pH-monitoring evidence of GERD tend to improve, but not resolve, with PPI therapy, whereas GERD-negative patients display little or no response [60], a result confirmed by a more recent meta-analysis [94]. PPIs might also improve symptoms related to atrial fibrillation and other supraventricular arrhythmias, especially after meal, in patients with proven GERD [95].

Despite the negative conclusions of a Cochrane meta-analysis [96], a recent review [97] suggests that a therapeutic benefit for acid-suppressive therapy in patients with chronic cough cannot be dismissed, advocating a rigorous patient selection that could allow the identification of patient subgroups likely to be responsive. On the contrary, no systematic reviews and meta-analyses [98-103] found any significant clinical benefit of PPI therapy over placebo in reflux laryngitis.

Asthma and GERD can often coexist, with reflux disease being reported in 40% to 80% of patients with asthma. While asthma medications can trigger GERD [104, 105], PPIs might on the contrary improve asthma control. Here again, an early Cochrane review [106] showed no benefit of PPI therapy on nocturnal symptom score and lung function, but a recent meta-analysis [96] – by selecting the morning peak expiratory flow (PEF) rate as primary outcome - disclosed a benefit of PPIs over placebo, which was greater in patients with proven GERD.

Despite the widespread use of PPIs in dental practice to manage the oral manifestations of GERD [107], treatment of dental erosions represents the only *objectively* documented clinical use [108].

In summary, while PPIs are the mainstay of medical treatment for esophageal manifestations of GERD, their benefit in extra-digestive GERD remains uncertain. The complexity of patient presentation is matched by the challenge in appropriate diagnosis of reflux as the cause for patients' symptoms, which may *also* be related to other co-morbidities. Upper GI endoscopy and pH monitoring suffer from poor sensitivity while laryngoscopy suffers from poor specificity in diagnosing reflux in this group of patients [109]. An empiric trial of PPIs could be the initial approach to diagnose and treat the potential underlying cause of these extra-esophageal symptoms. For those who improve with PPIs, GERD is presumed to be the aetiology, but for those who do not respond, diagnostic testing with impedance and/or pH monitoring are reasonable to exclude continued acid or weakly acid reflux. In such cases, aetiologies other than GERD may be pursued [109]. Difficult patients are best investigated and treated in referral centres.

5.3.2 Proton Pump Inhibitors for Eosinophilic Esophagitis

Summary of the current evidence*: PPIs are considered a first-line treatment in eosinophilic esophagitis (EoE). Other effective alternatives, such as dietary or topical corticosteroid therapy, should be used as second-line strategies, owing to long-term safety concerns (topical steroid therapy) and impairment of quality of life and nutritional inadequacy (dietary interventions). However, few data exist to guide specific recommendations on dose and duration of PPI initial therapy.*

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder, defined symptomatically by esophageal dysfunction and histologically by esophageal eosinophil-predominant inflammation [110, 111]. Originally thought to be a rare disease, its prevalence has greatly increased over the past 25 years. The allergic basis of EoE is supported by studies demonstrating that the underlying aetiology for EoE is likely an aberrant "antigenic" or "immune" response associated with consistent clinical and

histologic abnormalities [112], and by their disappearance after antigen-free amino acid-based elemental diet [113].

It is important to emphasize that esophageal eosinophilia is a histological finding that requires interpretation in the clinical context and that esophageal eosinophilia alone does not define EoE. Indeed, many other diseases have been associated with this histologic finding [114]. Although the presence of esophageal eosinophilia was first described in a subset of patients with GERD, it usually locates in the distal esophagus and never reaches the high density commonly observed in EoE, where it is associated with esophageal motor dysfunction, particularly dysphagia and food impaction [110, 111].

According to the ACG guidelines [115], PPI responsive esophageal eosinophilia (PPI-REE) should be diagnosed when patients have esophageal symptoms and histologic findings of esophageal eosinophilia, but demonstrate symptomatic and histologic response to PPIs. Originally categorized as a distinct clinical entity, PPI-REE is now considered a phenotype of EoE that is responsive to PPI therapy [110]. PPIs, therefore, no longer represent a diagnostic tool to distinguish between these two entities characterized by esophageal eosinophilia and symptoms, but a therapeutic option to be offered to patients with EoE. In this clinical setting, pH monitoring does not accurately predict response to PPI therapy [115], and similar remission rates have been documented in patients with both normal and pathologic pH monitoring [116]. In addition, symptom improvement is common with PPI therapy despite persistent eosinophilic infiltration [117].

A very recent meta-analysis [116], including 33 studies and 619 patients with EoE, found that PPI therapy led to a clinical response in 60.8% and histologic remission in 50.5% of patients. However, few data exist to guide specific recommendations on dosage and duration of PPI initial therapy. Retrospective data support the use of either once or twice daily use, but many of the PPI-REE studies used twice daily PPI dosing in the 20-40 mg range of the several available PPIs [115], for which there is a trend (albeit non significant) towards an increased effectiveness [116].

The reason for PPI responsiveness of this condition is not completely understood but could be due to other, non-antisecretory effects of PPIs [118], of which the anti-inflammatory action [119] is the most relevant one. Indeed, *in vitro* and *in vivo* studies suggest that the anti-inflammatory effects of PPI therapy rather than acid suppression alone may be responsible for this improvement through inhibition of the Th2-allergic pathway [120]. Indeed, like topical corticosteroids, PPIs down-regulated cytokine expression [121]. Alternatively, the dilated intercellular spaces (DIS) and consequent increased mucosal permeability, present in EoE [122], may allow allergen penetration, which triggers subsequent recruitment of eosinophils to the esophageal epithelium. Some studies have shown that DIS could recover after short-term PPI treatment in GERD (*for review see* [123]), a finding recently reported in patients with PPI-REE [124].

In summary, due to its safety profile, ease of administration and high response rates (up to 60% clinically), PPIs can be considered a first-line treatment for EoE. Recent data show that patients with EoE, responsive to topical steroids and diet, also respond to PPI treatment [125, 126]. However, the former approaches might be set aside as second-line, owing to long-term safety concerns (topical corticosteroid therapy) and impairment of quality of life or/and nutritional inadequacy (dietary interventions) [115, 116, 127].

5.3.3 Proton Pump Inhibitors for *Helicobacter pylori* (*H. pylori*) Eradication and Peptic Ulcer Disease

Summary of the current evidence*: PPIs represent a key component of any currently adopted regimens for* H. pylori *eradication. The degree and duration of acid suppression influence eradication rate. While almost all* H. pylori *positive ulcers are cured by* H. pylori *eradication*, H. pylori*-negative and NSAID/aspirin-negative peptic ulcers need high dose PPIs to be healed and, often, lifelong acid suppression is required to prevent recurrence.*

After the discovery by Warren and Marshall of the infectious aetiology of peptic ulcer (PU) disease in 1984 [128, 129], several lines of evidence confirmed that *Helicobacter pylori* eradication cures PU disease, without the need for subsequent long-term maintenance antisecretory therapy [130-133] and can also be beneficial to other *H. pylori*-related diseases [90]. While previously used only to heal peptic ulcers, PPIs have become a key component of all the currently adopted eradication regimens [134], gaining in that way a new role in the management of PU disease.

H. pylori is located within the gastric mucus layer, deep within the mucus-secreting glands of the antrum, attached to cells, and even within cells and is able to survive over a wide pH spectrum [134]. Since the survival capabilities of the *H. pylori* within the stomach make its eradication difficult, several different drug combinations have been developed, with variable and not consistent success, with no single therapy effective all over the world. Therefore, the search for a new regimen to treat *H. pylori* infection still continues today [135].

An effective therapy should therefore be able to eradicate the organism from each of these potential niches, which is an overwhelming task for any single antibiotic, whose in vitro susceptibility does not necessarily correlate with successful treatment in vivo. From the very beginning, it was recognized that therapy with a single antibiotic leads to poor cure rates and various recipes were attempted, resulting in several effective combinations of antimicrobials, bismuth, and antisecretory drugs [136].

PPIs display several pharmacological actions that give them a place in the eradication regimens, that is:

1. they exert an antibacterial action against *H. pylori* [137, 138];
2. by increasing intra-gastric pH, they allow the microorganism to reach the growth phase and become more sensitive to antibiotics such as amoxicillin and clarithromycin [139];
3. they increase antibiotic stability [140] and efficacy [141];

4. by reducing gastric emptying [142] and mucus viscosity [143], they increase the gastric residence time and mucus penetration of antimicrobials.

The mechanisms underlying the antibacterial activity of PPIs are complex and have been detailed in a comprehensive review [134]. These compounds are able to bind *H. pylori* cells and the bactericidal activity correlates with the degree of binding. Electron microscopy studies revealed – after exposure to a PPI – a significant change in the morphology of the microorganism, with appearance of coccoid forms (known to be degenerating organisms)[134]. PPIs are potent inhibitors of *H. pylori* urease at all pH values. This effect translates into significant reduction of ammonia production. Since this bacterial metabolite is important for development of mucosal inflammation and subsequent mucosal ulceration [144], patients receiving PPIs in combination with antimicrobials may have the additional benefit of reducing one of the potent inflammatory stimuli.

The inhibitory activity on *H. pylori* urease has been confirmed *in vivo.* As a consequence, PPI administration results in the inability to detect the microorganism, thus interfering with the urease-based diagnostic tests [90, 145]. The temporary inability to detect the presence of *H. pylori* is termed *suppression* and simply reflects a decrease in the number of organisms below the limits of detection [145]. It is worth mentioning that the infection affects the degree and the duration of acid inhibition achieved by antisecretory drugs. Amongst the mechanisms by which the microorganism could modify the pH-rising effect of PPIs, the buffering of *H. pylori*-generated ammonia on gastric acid remains the most convincing one [69]

A large clinical trial (the MACH-2 study) clearly showed that eradication rates achieved with two antibacterial agents (clarithromycin with either amoxicillin or metronidazole) are significantly lower than those achieved by the same two agents, given concomitantly with omeprazole [146]. These results were later confirmed by another RCT, where the combination of clarithromycin and tinidazole was evaluated with or without lansoprazole [147].

PPIs now represent the key component of any currently adopted regimens for *H. pylori* eradication, as recommended by Italian [148] and international guidelines [90, 149-151]. To be most effective, full dose PPIs should be given twice daily, concomitantly with antimicrobials as the mean intention-to-treat cure rates are greater in patients who use the high-dose PPI, compared with the standard-dose regimen [152, 153].

Eradication rates achieved with standard 1-week triple therapy (PPI-clarithromycin-amoxicillin) are dependent on CYP2C19 genotype [154]. Therefore, although any PPI can be selected, esomeprazole - and rabeprazole-based eradication regimens show the best efficacy [155]. The biological plausibility of their superiority over other members of the PPI-class relies on their catabolism. Indeed, esomeprazole, the S-enantiomer of omeprazole, being-together with its metabolite (esomeprazole sulphone) a powerful inhibitor of CYP2C 19, does inhibit its own metabolism, rendering all subjects “slow metabolizers” [156]. This results in a more consistent acid suppression and might underline the slightly higher eradication rates reported with these PPIs [155]. Conversely from the other PPIs, clearance of rabeprazole is much less dependent on CYP2C19 as it is predominantly metabolized non-enzymatically to rabeprazole thioether [157]. As a consequence, its antisecretory effect and the eradication rates of rabeprazole-based regimes are almost completely independent of genetic polymorphism [158]. As a matter of fact, a recent meta-analysis did show that – conversely from omeprazole and lansoprazole – the CYP2C19 genotype does not influence the eradication rate of esomeprazole and rabeprazole-based therapies [159].

The importance of profound and long-lasting acid suppression for *H. pylori* eradication is illustrated by two studies showing a significantly higher intragastric pH and lower percentage time spent at pH < 4 in patients successfully eradicated *versus* those who did not get rid of the bacterium [160, 161]. In addition, the eradication rate was higher in NAB-negative compared to NAB-positive patients [160]. Controlling intra-gastric acidity is therefore needed to achieve the best eradication rates [152, 162]. Indeed, some studies have shown that the use of high dose PPIs might results in high eradication rate even when one single antimicrobial agent is used [163-165]. The recent availability of more potent an

longer-acting acid suppressants, namely vonoprazan [5], may facilitate the use of a dual therapy (i.e. acid suppressant plus amoxicillin) [166].

Although *H. pylori* infection remains the single most common cause of peptic ulcer, an increasing proportion of patients have *H. pylori*-negative ulcers [167]. The proportion is higher in the USA (and likely in Australia) than elsewhere, being only 4% in Italy [168]. Although the precise aetiology of these ulcers is unknown, some are caused by the use of aspirin or NSAIDs [169]. Indeed, together, *H. pylori* infection and NSAID use account for approximately 90% of PU disease [170]. Patients with *H. pylori*-negative, NSAID/Aspirin-negative (idiopathic) ulcers may have a more serious ulcer diathesis. While NSAID ulcers can be healed with PPIs (s*ee below*), idiopathic ulcers are likely to require long-term management with acid-suppressing drugs. PPIs are again the drugs of choice, although the optimal duration of treatment is undefined and might be lifelong [171].

5.3.4 Proton Pump Inhibitors for Zollinger-Ellison Syndrome

Summary of the current evidence*: PPIs are the drugs of choice for the medical treatment of Zollinger-Ellison syndrome (ZES), but relatively high doses (3-4 times the standard dose) are required compared with those used in other acid-related conditions. Patients with complicated ZES (severe GERD, Billroth 2 resections, and MEN1 with untreated hyperparathyroidism) are more difficult to treat and usually benefit from twice-a-day PPI dosing. The intravenous route may be required initially. When curative tumor removal is not possible, antisecretory therapy must be continued* indefinitely. *Interruption of PPI treatment can have dangerous consequences.*

Zollinger-Ellison syndrome (ZES) is a rare disorder characterized by the presence of a gastrin-producing tumor (gastrinoma), which leads to sustained hypersecretion of

gastric acid and consequent peptic ulcer disease (often with complications such as perforation, bleeding, etc.), diarrhoea, or malabsorption. Gastrinomas usually develop in the non-beta islet cells of the pancreas or in the duodenal wall (40-90%). Up to two-thirds are malignant. About 20 to 25% of cases are seen in patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome [172, 173]. Although, even more rare, ZES symptoms may arise from a CCKoma [174], because both CCK and gastrin are full agonists for the gastrin–CCK_2 receptor of the parietal cell, whose stimulation drives gastric acid secretion.

Although somatostatin analogues (octreotide or lanreotide) can be used to reduce serum gastrin and gastric acid secretion [175-177], initial treatment is aimed at controlling the hypersecretion of gastric acid with an antisecretory drug. Dose titration using gastric acid analysis is the ideal way to best determine the lowest effective dose of medical therapy. Indeed, giving enough medication just to control symptoms is not considered adequate, and it is important that acid secretion is reduced below 10 mmol/hour (or below 5 mEq/h in the post-surgical stomach) to avoid ulcer recurrence and complications [178]. According to available guidelines [176, 177], a PPI is the drug of choice, but high doses (3-4 times the standard dose, once daily) are required compared with those used in other acid-related disorders. Patients with complicated ZES (severe GERD, Billroth 2 resections, and MEN1 with untreated hyperparathyroidism, etc.) are more difficult to treat and may require twice-a-day PPI dosing. The intravenous route (e.g. pantoprazole 80 mg every 8 hours [179] may be required initially. Once symptoms have been controlled, the tumor can be investigated for surgical excision [178]. When curative removal is not possible, antisecretory therapy must be continued *indefinitely*. In patients, who have undergone successful curative gastrinoma resection, PPIs may also be required because in more than half of them a hypersecretory state persists [180]. Interruption of PPI treatment (and consequent acid rebound) can have dangerous consequences, including severe peptic complications (strictures, perforations, etc.) [181]. Patient compliance to treatment is, therefore, crucial and should be regularly assessed. Over time, many patients could have the drug dose lowered [178].

The efficacy and safety of PPIs has revolutionized the management of ZES, so that total gastrectomy is no longer required. Long-term antisecretory treatment with PPIs has remained effective for > 10 years, without development of tachyphylaxis or any dose-related adverse effect [182]. Even in the high doses required for patients with ZES, PPIs have a notable record of safety. An analysis of ZES patients can provide important insights into some of the safety issues, concerning long-term acid suppression [183].

5.3.5 Proton Pump Inhibitors Therapy for Stress Ulcer Prophylaxis

Summary of the current evidence**:** *PPIs are the drugs of choice for acid suppression in stress ulcer prophylaxis (SUP). The risk of bleeding in intensive care unit (ICU) is reduced by some 60% in patients receiving SUP compared with those treated with placebo or no prophylaxis.* Routine *prophylaxis, however, is not justified by current evidence. SUP should be withheld in the majority of hospitalized patients, unless they have multiple risk factors since only those at risk of CIB are most likely to benefit from preventive strategies. Educating clinicians to follow SUP guidelines can improve the cost-effectiveness of PPI therapy in this clinical setting.*

Stress-related mucosal disease (SRMD, most commonly referred to as stress ulcer) is an acute condition that can be detected endoscopically in the majority (75-100%) of critically ill patients, within 24 hours of admission to an intensive care unit (ICU). However, the incidence of clinically important bleeding (CIB) from stress ulcer in the ICU population is low, the pooled figure from the most recent trials being some 1% [184]. The incidence has improved substantially over the recent decades, likely thanks to better overall ICU care. However, the mortality rate among patients with CIB was 48.5%, which is significantly higher than that (9.1%) of those without such bleeding [185], showing that stress-related mucosal disease can be a deadly condition.

Critically ill patients are at increased risk of developing SRMD and subsequent stress-ulcer bleeding as a result of both their underlying disease and therapeutic interventions. There are some well-established strong, independent risk factors for SRMD, respiratory failure and coagulopathy being the most relevant ones, with an OR of 15.6 and 4.3, respectively [184]. Other important factors are acute renal or hepatic failure, sepsis, hypotension, severe head or spinal cord injury, thermal injury involving more than 35% of the body surface area, acute lung injury, major surgery (lasting more than 4 hours) and history of GI bleeding [186].

Although no single study or meta-analysis has reported a decrease in the overall mortality related to stress ulcer prophylaxis (SUP), guidelines from the American Society of Health-System Pharmacists [187] and Surviving Sepsis Campaign [188] recommend routine prophylaxis with acid suppressive therapy for high-risk patients. The rationale for this recommendation relies on the finding that important GI bleeding is strongly associated with prolonged ICU stay and increased mortality [189]. Indeed, three large meta-analyses found that the risk of bleeding in ICU is reduced by some 60% in patients receiving SUP compared with those treated with placebo or no prophylaxis [190-192]. Therefore, SUP has become the standard of care in the ICU, sometimes irrespective of the presence of risk factors. The benefit of SUP using real-world data is however not easy to estimate because of the absence of a control group.

H_2RA have also been found effective in preventing CIB [186] and are the preferred acid lowering drugs in some ICUs [193] despite the efficacy of PPIs being significantly better. Over recent years, all meta-analyses [194-197] except one [198] confirmed the superior efficacy of this class of drugs. No studies showed a statistical significant difference in the rate of severe complications, such as nosocomial pneumonia since these associations were not reported outcomes in any of the RCTs assessed. A recent observational study [199] found that PPI treatment for SAP in critically ill patients is associated with a risk of *C. difficile* infection higher than that observed with H_2RAs (6.7% *versus* 1.8%).

SUP should be withheld in the majority of hospitalized patients, unless they have multiple risk factors [184, 186]. Indeed, as outlined by current practice guidelines [187, 188],], any risk factor different from the above mentioned does not predispose independently a patient to stress ulcer bleeding. In addition, a recent meta-analysis [200] suggests that - in patients receiving enteral nutrition - SUP may not be required. In addition, its implementation might be associated with an increased risk of infectious complications, such as nosocomial pneumonia and C. difficile-associated diarrhoea. Furthermore, patients with liver cirrhosis may actually have an increased mortality rate if treated with PPIs [201].

Nevertheless, several studies demonstrate that in many non-ICU patients, lacking an indication for SUP, acid suppressive therapy is started upon hospital admission [202]. A recent study [203] - while confirming that PPI use for SUP has spread inappropriately to low-risk patients - found that more than 50% of admitted PPI users were inadvertently prescribed a PPI at discharge, without a real medical need for acid suppression.

In summary, PPIs represent the drugs of choice for acid suppression in SUP. However, *routine* prophylaxis is not justified by current evidence. Only patients at risk of CIB are likely to benefit from preventive strategies. Educating clinicians to follow SUP guidelines can improve the cost effectiveness of PPI therapy in this clinical setting.

5.3.6 Proton Pump Inhibitors Therapy for Dyspepsia

Summary of the current evidence: *PPI therapy in both uninvestigated and functional dyspepsia is widespread. Indeed, these drugs represent a key component of all the currently employed* Helicobacter pylori *eradication regimens. The search for and eradication of the infection is the first line therapy in the young dyspeptic patient without alarm symptoms. In those patients with persisting symptoms despite successful eradication or naïve-uninfected patients with epigastric pain syndrome (EPS), short-term 4-8 weeks PPI treatment should be attempted. Finally, PPI co-therapy is indicated in patients with NSAIDs associated dyspepsia, also with the aim of preventing GI events.*

Dyspepsia is a common GI condition seen in clinical practice. It is not a single disease, but rather a complex of symptoms referable to the upper GI tract that often overlaps with other disease entities. In front of a patient with dyspeptic complaints, physicians should carefully evaluate the history and perform a physical examination in order to assume that symptoms arise from the upper GI tract [204]. If the patient is young (< 45 years), and there are no alarm symptoms, endoscopy and/or functional investigation are usually not performed, the condition is labelled as "uninvestigated" dyspepsia and treatment is empiric. On the contrary, if endoscopy does reveal a structural abnormality, management of dyspepsia relies on treatment of the underlying disease (*e.g.* peptic ulcer, reflux esophagitis, or malignancy). When endoscopy is negative (which is the case in more than 70% of patients dyspeptic symptoms), "functional" dyspepsia (FD) could be considered and, provided Rome IV criteria are fulfilled [205], the final diagnosis can be confirmed [204].

FD is characterized by a continuous or frequently recurring epigastric pain or discomfort centred in the upper abdomen for which no organic cause can be determined. Accordingly with the most updated Rome IV classification, dyspepsia is subdivided into postprandial distress syndrome (PDS; including fullness, early satiety, nausea) and epigastric pain syndrome (EPS; including epigastric pain or epigastric burning) [205]. However, symptom overlap with either GERD or irritable bowel disease (IBS) is not infrequent [206, 207].

FD is widely prevalent in the general population – up to 15% in Italy [208] – so that FD patients are frequently managed in clinical practice by both general practitioners and gastroenterologists. Since the etiology of FD remains unclear and is probably heterogeneous, no definite single treatment is currently available for these patients [204]. Indeed, different therapeutic approaches have been proposed.

Since some drug classes (e.g. NSAIDs, calcium channel blockers, corticosteroids, ACE inhibitors, and methylxanthines) can induce dyspeptic symptoms [209], a careful evaluation of the current drug therapy is of paramount importance. Those *dyspeptogenic* compounds should be withdrawn whenever possible. In patients with NSAID-associated dyspepsia, PPIs are effective and should be given also with the aim of preventing adverse GI events (*see below*).

The role *H. pylori* in FD is supported by data from a meta-analyses showing that *H. pylori* eradication had a statistically significant benefit compared with placebo (RR of remaining dyspeptic 0.90; NNT: 13) [210, 211]. However, *short-term* benefit is often not evident, since symptoms relief becomes significant only 6 months after successful cure of the infection [212]. PPIs represent a key component of all the commonly used eradication regimens (triple, quadruple and sequential therapies).

It has been estimated that *H. pylori* 'test and treat' strategy is cost-effective in those regions where prevalence of the infection is >20% [213], as in Italy, and that the advantage persists at long-term follow-up [214, 215]. Unfortunately, no predictive factors for clinical benefit have been identified, so that eradication treatments should be attempted in all dyspeptic patients. *H. pylori* should be investigated with either non-invasive tests or upper endoscopy, according to the age of the patient and the presence of alarm symptoms [148].

In patients with dyspeptic symptoms persisting despite successful eradication or naïve uninfected patients with EPS, PPI therapy can be attempted, an approach achieving a success rate of 34% (NNT 10, 95% CI: 7-33) [216]. PPIs are particularly effective when overlapping reflux symptoms are present, while no significant benefit occurs in dyspeptic with PDS [217]. It is worth emphasizing that the effect of PPIs in FD occurs at standard doses and, as meta-analysis found no dose-response effect [216, 217], escalating the dose in non-responders to standard doses should not be considered. If breakthrough symptoms occur, antacids or alginate-containing formulations may be used [216].

Conversely from GERD, a long-term therapy with PPIs in FD is not indicated [217]. After successful treatment, a tapering strategy rather than abrupt discontinuation is preferred [217]. Although symptoms may recur in nearly 70% patients within 1-year follow-up [82], re-starting treatment only in these patients is more advantageous than a continuous and expensive treatment, prescribed in all cases.

Dyspeptic symptoms are common in GERD patients, especially those with frequent reflux related symptoms. In these patients, epigastric pain, belching, bloating, and early satiety were found to improve on PPI therapy, conversely from nausea e vomiting, which did not benefit from acid suppression [218].

In addition to suppressing acid secretion, PPIs can also inhibit gastric motility and delay emptying rate [219], and – as a consequence - dyspeptic symptoms may actually be worsened by PPI therapy or, alternatively, new symptoms (especially postprandial fullness) may arise during treatment. If this is the case, patients could be switched to the H_2-RAs, ranitidine or nizatidine, which – in addition to their antisecretory activity - display a cholinergic-like activity [219] and have been shown to accelerate gastric emptying [220]. On the other hand, the Cochrane meta-analysis [216] showed that H_2RAs are better than placebo in obtaining symptom relief in patients with FD.

5.3.7 Proton Pump Inhibitors for NSAID-Associated Symptoms and Lesions

Summary of the current evidence: *Standard dose PPIs are indicated for patients taking non-selective, non-steroidal anti-inflammatory drugs (ns-NSAIDs) at risk for upper GI complications (bleeding and perforation) and for those given selective COX-2 inhibitors, who have had an episode of previous GI bleeding. . In both non-selective and COX-2 selective NSAIDs users PPI therapy reduces upper GI symptoms, in particular dyspepsia. However, NSAID-induced adverse events in the lower GI tract are not prevented by PPIs.*

Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used classes of drugs. Although they are very effective medications, their use is associated with a broad spectrum of adverse reactions in the liver, kidney, cardiovascular (CV) system, skin and gut [221]. Gastrointestinal (GI) adverse effects are the most common and include a wide clinical spectrum ranging from dyspepsia, heartburn and abdominal discomfort to more serious events such as PU with life-threatening complications, including bleeding and perforation [222].

Since symptoms are not a reliable indicator of mucosal damage, it is important to identify factors that predict the risk of GI events in NSAID users. The risk factors for upper GI bleeding (UGIB) associated with NSAID use have been well defined by several studies [222]. Among them, the most important are prior history of complicated ulcer and age. Older age is common in NSAID users and those aged >65 years carry a risk similar to those with a history of peptic ulcer. Advancing age increases the risk by about 4% per year, probably because of the presence of other associated risk factors [223]. The presence of multiple risk factors greatly increases the risk of GI complications [222]. The role of *H. pylori* infection in patients taking NSAIDs and the potential benefit of eradication on upper GI risk in infected NSAID users has been controversial. However, eradication of associated *H. pylori* infection is beneficial when starting treatment with NSAIDs or aspirin, especially in the presence of an ulcer history [90, 224].

An often forgotten, risk factor for upper GI complications is represented by drug combinations with NSAIDs [225]. While the role of steroids, antiplatelet drugs and anticoagulants is long known, the synergistic effect of selective serotonin receptor inhibitors (SSRIs) has until recently been overlooked. Over the past 15 years, several epidemiologic studies, summarized by three recent meta-analyses [226-228], have shown an association between SSRI use and the occurrence of UGIB, and found that this risk is further increased among patients, who concomitantly use NSAIDs [229, 230] or/and hold *H. pylori* infection [231], while it is lowered by concomitant PPI intake [227, 232]. The most plausible mechanisms underlying this detrimental effect include a marked decrease in

serotonin platelet content, with consequent impairment of platelet aggregation in response to injury and prolongation of bleeding time as well as an increase in gastric acid secretion, with potential ulcerogenic activity [233, 234]. When given with NSAIDs, SSRIs may inhibit their metabolism, raising their blood levels and – through impairment of the hemostatis - may promote more severe bleeding. Since the concomitant use of both these drugs results in a significantly higher risk of UGIB than either drug alone [229, 230], this combination should be avoided whenever possible and, if not avoidable, an adequate gastroprotection be adopted from the very beginning [235].

GI symptoms usually develop within the first few days of starting a NSAID therapy and can actually occur with the first dose of the drug. Although some studies have suggested that the first 2 months of treatment represents the period of greatest risk for complications with a relative risk of 4.5%, available evidence (from both RCTs and observational studies) shows that the risk of GI complications is constant over time, either during short-term or long-term NSAID use [170]. Therefore, even a short course of NSAID therapy (e.g. for postoperative pain or acute musculoskeletal injury) carries a risk of GI complications similar to that of long-term treatment. As a consequence, prevention strategies should be implemented regardless of the duration of therapy, especially in patients with more than one risk factor (i.e. at high GI risk).

All the RCTs have shown that PPIs are more effective than H2-RAs either in preventing and treating gastro-duodenal lesions [236]. The reasons underlying the superiority of this class of antisecretory drugs has been clarified by preclinical and clinical pharmacological studies, pointing out that degree and duration of acid inhibition are both important factors in determining their efficacy in prevention of NSAID-injury [237]. They also reduce upper GI symptoms associated with ns-NSAID and coxib use [236]. Due to the long half-life and entero-hepatic circulation of many NSAIDs, a split dose PPI might be useful. There is, however, no evidence for the clinical usefulness of this regimen.

COX-2 selective NSAIDs (often incorrectly referred to as coxibs[1]) have an improved upper GI safety profile compared to traditional (non-selective) compounds, as extensively shown in endoscopy and clinical outcomes studies [239-241]. The evidence is strong, with consistent reductions in events of about 50% in large RCTs, meta-analyses of RCTs and large observational studies in clinical practice [239]. Among patients with a prior ulcer bleed, treatment with a COX-2 inhibitor or a ns-NSAID plus PPI is still associated with a clinically important risk of recurrent ulcer bleed (some 10%) [222]. In these patients, the combination of a PPI and a COX-2 inhibitor reduces the risk of upper GI bleeding from that of COX-2 inhibitors alone [236]. A very recent network meta-analysis found indeed that this drug combination represents the best strategy to prevent ulcer complications [242].

In addition to the upper GI tract, the NSAID-induced damage extends beyond the duodenum. Since NSAID-induced intestinal damage involves non-acid related mechanisms [222], co-administration of PPIs does not prevent NSAID-induced intestinal damage but might actually aggravate it [28, 170, 243, 244], most likely by inducing dysbiosis [245]. Furthermore, NSAID-associated lower GI bleeding is not prevented by PPI co-administration [246].

While the better upper GI safety of COX-2 selective agents over traditional NSAIDs is well established, their individual lower GI tolerability is less well evidenced and appears to differ. Both endoscopic and video-capsule studies have shown that celecoxib displays a better intestinal tolerability compared to an NSAID plus a PPI [28]. The good upper and lower GI safety profile was confirmed by the large CONDOR and GI-REASONS trials [28]. However, this benefit is partially lost when this COX-2 selective inhibitor is combined with a PPI [244].

[1] The term “coxib” is being used in the medical/scientific literature as synonymous of “selective COX-2 inhibitor”, which is not the case. The term “coxib” is a World Health Organization term used to describe a *chemical* class. It does not describe any pharmacological activity, nor indicate anything regarding COX-2 selectivity. Actually, there are members of the coxib family (e.g. SC-560) that selectively inhibit COX-1 238. Wallace JL. Selective cyclooxygenase-2 inhibitors: after the smoke has cleared. Dig Liver Dis. 2002; 34: 89-94.

On the other hand, over the recent years, great attention has been focused on CV adverse effects of COX-2 selective inhibitors, which prompted a re-evaluation of the CV (and global) safety profile of traditional NSAIDs. Current evidence suggests that non-selective and COX-2 selective inhibitors display a similar incidence of these adverse effects, but with molecule-specific quantitative differences between the various drugs [247, 248].

NSAIDs are an essential part of the therapeutic armamentarium despite their well characterized GI and CV risk profiles. Physicians should not prescribe NSAIDs before taking a careful history and doing a physical examination so that they can acquire the information they need to balance risks and benefits for individual patients. When GI and/or CV risk factors are present appropriate preventive strategies (i.e. COX-2 selective inhibitors and/or PPI use as well low-dose ASA) should be implemented from the very beginning and compliance to treatment assessed regularly, especially in the elderly [222]. Finally the appropriateness of an NSAID prescription should be emphasized, i.e. to control inflammation and pain, rather than to control pain alone [249]. Only then can we hope to limit the expanding NSAID epidemic.

5.3.8 Proton Pump Inhibitors for Corticosteroids Users

Summary of the current evidence**:** *Corticosteroid therapy does not cause damage to the gastro-duodenal mucosa, but can enhance the GI risk of NSAIDs. Therefore, unless patients taking corticosteroid therapy have a peptic ulcer or are under concomitant NSAID therapy, mucosal protection with a PPI is not routinely indicated.*

Conversely from NSAIDs, corticosteroids do not cause any direct injury to the gastro-duodenal mucosa [250]. Some experimental evidence actually suggests a mucosal protective effect [251, 252]. These drugs may however increase the GI risk of NSAID therapy and may hamper the healing of idiopathic or iatrogenic ulcers [253]. The association

between corticosteroid use and GI adverse events in patients with risk factors other than NSAID use remains controversial. Indeed, some studies reported an increased risk of peptic ulcer complications in corticosteroid users, while other investigators failed to demonstrate such an association, after adjustment for confounding factors [254-258]. A meta-analysis failed to show any significant risk for gastric or duodenal ulcers in patients receiving corticosteroids treatment compared to controls [259]. It is worthwhile emphasizing that the design of the studies included in the meta-analysis was quite heterogeneous as was the type of patients selected (outpatients or inpatients, presence of comorbidity and co-therapy) as well as peptic ulcer definition. However, a systematic review of meta-analyses as well as case-control studies reached the same conclusion [260].

A more recent systematic review and meta-analysis of 159 studies, published between 1983 and 2013, on GI bleeding and perforation in corticosteroid users [261] found that corticosteroid therapy may increase the risk of GI events (OR: 1.43) *only* in the hospitalized patients. Here again, the diversity of GI bleeding definitions (widely varying from occult blood in stool to bleeding requiring transfusion or hospital stay) as well as the heterogeneity of the patients included do not allow drawing clinically relevant conclusions [261]. Taking these considerations into account, no evidence currently supports PPI therapy as prophylaxis for corticosteroid use, in the absence of concomitant NSAID therapy.

In summary, PPI co-therapy is not routinely indicated in patients taking corticosteroids unless they have a history of peptic ulcer or are taking NSAIDs. In hospitalized patients on corticosteroid therapy, prophylaxis against stress ulcers could be limited to those with a history of peptic ulcer, clotting impairment or requiring mechanical ventilation for more than 48 hours [262]. Despite corticosteroids increase the risk of GI bleeding in patients with either diverticular disease of the colon or acute ischemic stroke [263, 264], PPI therapy is not expected to exert any preventive effect on eventual drug-induced GI bleeding in these patients.

5.3.9 Proton Pump Inhibitors in Anti-Platelet or Anti-Coagulant Therapy

Summary of the current evidence**:** *Standard dose PPI therapy is advised for gastro-protection in all patients on anti-platelet therapy, who are at increased risk of gastrointestinal bleeding (age >65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer). INR monitoring is required when starting or stopping PPI therapy in vitamin K antagonist users. In patients receiving clopidogrel or vitamin K antagonists, choosing PPI lacking interference with the hepatic CYP450 enzymes might be preferred. No demonstrated interaction exists between PPIs and the novel oral anticoagulants.*

Based on a documented efficacy, anti-platelet therapy (aspirin <300 mg/daily; ticlopidine 100 mg/daily, clopidogrel 75 mg/daily) is widely used for both primary and secondary prevention of cardiovascular and cerebrovascular ischemic events [265, 266]. However, anti-platelet drugs may cause adverse GI events (gastroduodenal ulcerations/erosions, overt bleeding, occult bleeding, and - only seldom – a perforation), with a definite probability of death, particularly in the elderly [267]. Therefore, gastroprotection is advised in those patients at increased GI risk during anti-platelet therapy. Increased risk factors include age >65 years, concurrent use of steroid/anticoagulant therapy, or history of peptic ulcer [222, 256, 268-270]. Presence of relevant co-morbidities (heart failure, renal impairment, stroke, diabetes, on-going malignancy) and smoking are additional risk factors for both GI events and related mortality [256, 269-271]. Standard PPI-dose is the most effective gastro-protective therapy [272, 273]. Regrettably, PPI therapy is not effective in preventing bleeding lesions in either small intestine or colon induced by anti-platelet drugs, for which no protective strategies are today available [270, 274, 275].

A matter for concern is the interaction between PPI and clopidogrel. Based on pharmacokinetic studies, PPI therapy reduces the efficacy of clopidogrel by interfering

with the hepatic CYP2C19-based activation [276]. However, the clinical relevance of such a phenomenon is largely controversial. Indeed, a panel of experts of European Society of Cardiology recently suggested that there is no conclusive evidence to discourage PPI use with clopidogrel due to a potential increased risk of ischemic events [277]. Indeed, the only prospective study (the COGENT trial) demonstrated that omeprazole significantly reduces the rate of composite GI events but did not show any increase in the composite CV events in patients at high CV risk [278]. Furthermore, a recent meta-analysis [279], while confirming that the pharmacodynamic interaction between PPI and clopidogrel has no clinical significance, actually suggests that PPIs are a marker of increased CV risk in patients taking clopidogrel rather than a direct cause of worse outcomes. Nevertheless, PPIs that lack of inhibition of CYP 2C19 (i.e. pantoprazole or rabeprazole) might be preferred in clopidogrel users [277]. No significant interaction between PPIs and the new antiplatelet agents (prasugrel or ticagrelor) has been documented [277].

Co-administration of aspirin and clopidogrel is associated with synergistic effects in causing serious GI bleeding. Indeed, epidemiological studies have invariably shown that combination of two antiplatelet drugs produces significant excess risk of UGIB [225, 280]. PPI co-treatment is also effective in reducing the risk of UGIB in patients receiving dual antiplatelet therapy [281, 282]. It is worthwhile mentioning that – among patients with dual antiplatelet therapy and PPI co-therapy – GI bleeding episodes are more frequent in the lower GI tract [283]. This changing pattern of bleeding likely reflects the success of gastroprotection [284].

Anticoagulants, either vitamin K antagonists (VKAs) or novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban and apixaban, do not cause *per se* gastroduodenal mucosa injury. These medications may, however, facilitate bleeding of pre-existing peptic ulcers. While gastroprotection is generally not advised, unless a concomitant anti-platelet or NSAID therapy is prescribed, a very recent retrospective cohort study found that PPI co-therapy is associated with reduced risk of warfarin-related upper GI bleeding. As expected, the risk reduction was greatest in patients taking

also antiplatelet and/or NSAIDs, but was still significant in those without concurrent use of these medications [285].

It is worth mentioning, however, that – in patients under acid suppression because of gastroprotection or any acid-related disease - intensified INR monitoring is recommended since PPIs may potentiate VKA-induced anticoagulation, most likely due to facilitated gastric absorption of warfarin [277]. When acenocoumarol is used as an anticoagulant, some caution is needed when prescribing PPIs (in particular omeprazole, esomeprazole and lansoprazole) because of potential drug-to-drug interaction [286]. No clinically significant interaction during PPI and NOAC co-administration occurs, so that dabigatran-related dyspepsia may be safely treated with PPIs [277].

5.3.10 Proton Pump Inhibitors for Treatment of Peptic Ulcer Bleeding

Summary of the current evidence: *Endoscopy is the mainstay of treatment of peptic ulcer bleeding. However, PPI therapy - after endoscopic hemostasis - reduces the risk of re-bleeding, requirement for surgery and mortality in high-risk patients. Pre-endoscopic administration of a PPI can be useful in downgrading stigmata of recent hemorrhage, thereby reducing the need for endoscopic hemostatic procedures.*

The goal of medical therapy for bleeding ulcers has been traditionally to aim maintaining a sustained intragastric pH (>6 units), in order to promote platelet aggregation as well as clot formation and stability [287, 288]. Indeed, platelet function is impaired at low pH [289], and pepsin promotes clot lysis below pH 5 [290].

Although endoscopic therapy is able to achieve hemostasis in most patients, recurrent bleeding is not uncommon [291, 292]. Several meta-analyses [293-295] have shown that adjuvant treatment with a PPI after endoscopic hemostatic therapy reduces the risk of re-bleeding and the requirement for surgery after ulcer bleeding but has no benefit on

overall mortality, an effect seen only in Asian trials and in patients with active bleeding or a non-bleeding visible vessel. In addition, treatment with a PPI produces small, but potentially important, reductions in transfusion requirement and length of hospitalization[296, 297]. Although current guidelines [298-300] recommend a regimen of an intravenous (i.v.) bolus followed by a *continuous* infusion of PPIs, a recent meta-analysis [301] found that the efficacy of continuous and *intermittent* PPI therapies were comparable. Whether low-dose or oral PPIs can substitute, high-dose PPIs after endoscopic hemostasis is controversial. In a recent meta-analysis from Taiwan [302], investigators concluded that low-dose and high-dose regimens were equivalent. However, they included trials with a small number of patients and patients with ulcers showing low-risk stigmata or even clean-base ulcers. Similarly, some trials [303, 304] reported that the efficacy of oral PPIs is comparable to that of intravenous PPIs, but the results were combined from open-labelled trials with limited sample size. Furthermore, *different* oral regimens were combined together and compared with *different* intravenous regimens. It is also worth mentioning that most studies included in this setting have been performed in Asian patients [305].

Currently available PPIs are not able to maintain the intragastric pH above 6 for prolonged periods [306]. As a consequence, intravenous infusion has often been used in clinical studies. Intravenous esomeprazole is faster and more effective in raising intragastric pH than i.v. lansoprazole[307] or i.v. pantoprazole [308-310]. Even by the oral route, esomeprazole 40 mg, which provides the most effective control of intragastric pH amongst the class [54, 55] achieves greater acid inhibition than intravenous pantoprazole (40 mg/daily) on both day 1 and day 5 [311]. The Peptic Ulcer Bleed study, involving 91 hospital emergency departments in 16 countries, showed that high-dose intravenous esomeprazole (80 mg, followed by 8-mg/h infusion, over 72 hours), given after successful endoscopic therapy to patients with high-risk stigmata of peptic ulcer bleeding, reduced recurrent bleeding at 72 hours and had sustained clinical benefits for up to 30 days while patients were on maintenance oral esomeprazole (40 mg daily) [312].

PPI treatment, initiated prior to endoscopy in patients with upper GI bleeding, significantly reduces the proportion of patients with stigmata of recent hemorrhage at index endoscopy: pooled rates were 37.2% and 46.5% respectively (OR: 0.67) [313, 314]. Although there is no evidence that PPI treatment affects clinically important outcomes (mortality, re-bleeding or need for surgery), pre-hospital (oral or intravenous) administration of a PPI could downgrade high-risk stigmata of recent hemorrhage. This might increase the success of endoscopic hemostatic therapy and/or reduce the requirement for it.

5.3.11 Proton Pump Inhibitor in Patients with Cancer

Summary of the current evidence: *In cancer patients, PPI use could be indicated to treat or/and prevent chemotherapy-induced GERD and gastro-duodenal ulceration, with accompanying symptoms. Patients with GI mucositis or dysphagia might also benefit from these drugs. Due to the low number or poor quality of the available studies, the evidence supporting these indications is low.*

Amongst the adverse effects of cancer chemotherapy, GI symptoms are the most common and have the greatest impact on the quality of life [315-317]. Fewer than 20% of affected patients are referred to a GI specialist [318] because clear management algorithms and routine referral pathways are not in place, due to limited research in this topic. As a consequence, some treatable symptom complexes go unrecognized or/and ineffective and potentially harmful treatments are prescribed. Sometimes, persistent symptoms do compromise or prevent ongoing anticancer treatment.

While several guidelines for management of the GI adverse effects of cancer chemotherapy do exist [319-325], only the ESMO [319] and MASCC/ISOO [325] or clinical practice recommendations address gastro-esophageal mucositis. Different types of cancer therapy alter the integrity of the GI mucosa [326] as well as the microbial flora that inhabit

the oral cavity and the gut [327]. These treatments also affect the amount and composition of saliva [328]. In addition, they negatively impact on epithelial turnover and maturation, leading to impairment of mucosal barrier [326]. Up to 40% of patients undergoing treatment with gemcitabine or S-1 (an oral pro-drug of 5-FU) for pancreatic cancer complained of GERD-related symptoms [329], and endoscopy revealed the presence of severe mucosal lesions (multiple gastric erosions, diffuse erosive gastritis, gastric or duodenal ulcer) in 46 % of patients after a single cycle of chemotherapy (with cisplatin plus etoposide) [330]. Gastro-duodenal ulcers are extremely frequent (up to 100%) in patients submitted to hepatic intra-arterial chemotherapy [331, 332]. Even the more recent molecular-targeted agents are not devoid of GI adverse events [333]. For instance, ulceration and perforation of the stomach and bowel are well-known complication of bevacizumab (a humanized monoclonal antibody against vascular endothelial growth factor) [334, 335].

The rationale for acid suppression in patients undergoing cancer chemotherapy stems from the evidence that cytotoxic treatment damages the gastro-esophageal mucosa, without affecting the acid producing capacity of parietal cells. Therefore, mucosal damage may result – at least in part – from the effect of an aggressive acid-peptic secretion on an already damaged mucosa [336]. British guidelines [321] suggest PPI use - amongst other therapeutic options - in the management of dysphagia and/or retching induced by cancer chemotherapy, but do not provide any indication about the dose and treatment duration. Acid suppression appears to be beneficial in the treatment of GI mucositis induced by chemotherapy [337] and radiation [338], while once daily PPIs seem to improve chemotherapy-induced GERD symptoms [329], but data are conflicting. Two large clinical trials [339, 340] have shown PPIs to be effective in the prevention of chemotherapy (CMF or 5-FU) induced gastro-duodenal injury and reducing the incidence of heartburn and epigastric pain. In the more recent study [340], omeprazole was also highly effective in preventing delays in cancer treatment. No postponement of chemotherapy was required for patients treated with PPIs, who received the PPI, while chemotherapy was delayed in some patients receiving placebo or an H_2RA.

Several other indications for PPI use in cancer patients have been suggested and/or proposed [341]. They include postoperative symptom relief in patients after gastric or oesophageal resective surgery, prophylactic use in patients treated with NSAIDs as analgesics in cancer pain, acute management of upper gastrointestinal bleeding in patients with proximal GI cancer, prophylactic use in patients treated with palliative upper GI endoscopic stenting, prophylactic use in cancer patients who are at high risk for PU disease. However, most of the above indications have not been formally tested in specific, well-designed RCTs. In addition, even for those evaluated in clinical studies (i.e. chemotherapy-induced GERD symptoms or gastro-duodenal ulceration), the evidence is low and often derives from single studies or single centres. Nevertheless, up to 73% of patients admitted to oncology or hematology units are treated with acid suppressants (PPIs or H_2RAs) [342, 343], mostly for SUP or unspecified *gastroprotection.*

The Globocan survey [344] indicates that in 2012 approximately 32.6 million people were living with cancer (within 5 years of diagnosis). It is therefore astonishing and disappointing that thousands of studies, often dealing with trivial GI symptoms and spending billion euros, have been performed while very few evaluated the potential indications of PPIs in cancer, to provide physicians with the best way to cope with the GI adverse effects of chemotherapy or radiotherapy and relieve the suffering of these difficult patients.

Besides the several potential and alleged indications of PPIs in cancer patients, increasing evidence suggests for this class of drugs an anti-tumor effect (through the selective induction of apoptosis as well as an anti-inflammatory effect) [345]. They also exert a protection of cancer cells from developing chemo- or radio-therapeutic resistance [346]. Acidification of extracellular compartment represents a conceivable mechanism of drug resistance in malignant cells. In addition, it drives proliferation and promotes invasion and metastasis [346]. Experimental evidence has shown that PPIs counteract tumor acidification (*via* inhibition of vacuolar H^+ ATPase) and restore sensitivity to anticancer drugs. Moreover, early clinical data have supported their role – *as add-on medications* - to anticancer treatments in patients with osteosarcoma or

breast cancer [347]. A recent large epidemiological study (the SPORE program [348]) found that patients with head and neck tumors, taking acid suppressants, had significantly longer overall survival compared to those, who did not. Specifically designed clinical trials are ongoing to better characterize the role of PPIs as new therapeutic agents in cancer treatment. For these reasons, at the current status of the present knowledge, PPIs use as adjunct to cancer chemotherapy should not be used outside a clinical trial.

5.3.12 Proton Pump Inhibitors Use in Cirrhosis

Summary of the current evidence**:** *PPI use in patients with liver cirrhosis must be very cautious since there is no evidence of benefit except for downgrading esophageal ulcers after sclerotherapy or banding of esophageal varices. There is also some evidence that their use could be associated with development of spontaneous bacterial peritonitis.*

In clinical practice, PPI therapy is often used in cirrhotic patients, in the absence of acid-related disease, to prevent bleeding from hypertensive gastropathy [349]. This approach is not evidence-based and therefore not justified, also taking into account that acid secretion is markedly reduced in these patients [350].

A systematic review, performed in 2008, was unable to find any randomized clinical trials on acid-lowering drugs in the prevention of esophago-gastric variceal bleeding in cirrhotic patients. It is therefore not possible to establish whether these drugs are beneficial or harmful in this setting [351]. It is worth mentioning, however, that PPI use is associated with a microbiota shift and functional changes in the distal gut of patients with compensated cirrhosis, an effect that could drive or aggravate the pre-existing small intestine bacterial overgrowth (SIBO)[352, 353] .

The only indication of PPIs, which is by the way weakly evidence-based, is the prevention and/or treatment of esophageal ulcers after sclerotherapy or variceal band ligation. The best available evidence supports the short-term use (maximum 10 days) of PPIs to reduce ulcer size, provided spontaneous ulcer healing is a concern. Practices such as high dose infusion and prolonged use should be discouraged until evidence of benefit become available [354].

When prescribing PPIs to cirrhotics, the benefit-to-risk ratio must be carefully evaluated. Indeed, PPI therapy seems to be a risk factor for the onset of spontaneous bacterial peritonitis (SBP). A meta-analysis [355] showed that – compared to cirrhotic patients not receiving PPIs – those taking these drugs had an increased risk (N = 3815; OR: 3.15; 95% CI = 2.09–4.74) of developing SBP, an effect more evident in case-control studies than in cohort studies [356]. Another recent systematic review [357] also found an increased *overall* risk of bacterial infections (OR: 1.98). A more recent case-control study discovered the PPI use in cirrhotic patients increases the risk of development of hepatic encephalopathy in a dose-dependent fashion [358]. All these analyses were mainly based on retrospective studies. The only large, multicentre, prospective trial [359] with PPIs dealt with SPB and found acid suppression not associated with an increased risk. Further studies are therefore needed to better clarify these clinically relevant issues.

5.3.13 Proton Pump Inhibitors for Pancreatic Diseases

Summary of the current evidence: *PPIs do not affect the clinical course of acute pancreatitis (AP), such as the length of hospitalization and time to starting oral intake or pain relief and, as a consequence, they are not recommended routinely in this clinical setting. However, their use – as* add-on *medication to enzyme replacement therapy (ERT) – is indicated in patients with chronic pancreatitis (and other diseases characterized by exocrine pancreatic insufficiency), whose steatorrhea is refractory to ERT.*

Acute pancreatitis (AP) is one of the most common GI disorders, requiring acute hospitalization worldwide, with a reported annual incidence of 13-45 cases per 100,000 persons [360]. AP is an inflammation of the pancreas; it is sometimes associated with a systemic inflammatory response that can impair the function of other organs or systems. The inflammation may subside spontaneously or may progress to necrosis of the pancreas and/or surrounding fatty tissue. The dysfunction may resolve or may progress to organ failure. As a consequence, there is a wide spectrum of disease from mild, where patients recover within a few days, to severe (10-15%) with prolonged hospital stay, the need for critical care support, and a 15-20% risk of death [361, 362]. In Italy, AP is more commonly a mild disease with a biliary aetiology and a low (5%) overall mortality rate [363]. Whatever the cause, it should be recognized that AP is a systemic disease and not simply as a disease of the pancreas. Thus, this common, potentially deadly, condition requires up-to-date evidence-based treatment.

AP is characterized by pancreatic and peri-pancreatic fat injury in part mediated by autodigestive enzymes. Excessive stimulation of the exocrine pancreas was long thought to worsen AP [364] and this represented the rationale for using inhibitors of exocrine pancreatic secretion (e.g. somatostatin and its analogs) as potential therapies for AP [365]. Along the same lines, antisecretory agents might be able - *via* inhibition of acid secretion and secretin release, due to duodenal acidification [366] - to contribute to the inhibition of pancreatic secretion.

Despite omeprazole is unable to inhibit amylase release from isolated pancreatic acini [367], pantoprazole appears capable of reducing tissue infiltration of inflammatory cells and acinar cell necrosis in rats with experimentally-induced pancreatitis [368], an action likely mediated *via* a reduced expression of inflammatory and adhesive proteins, key mediators in the pathogenesis of AP. The only clinical trial to date [369] found that treatment with pantoprazole does not affect the clinical course of AP, such as the length of hospitalization and time to starting oral intake or pain relief. In addition, two retrospective studies found that PPI use does not affect clinical outcomes of patients

with severe AP [370] or prevent post-ERCP pancreatitis [371]. As a consequence, most International Guidelines on the management of AP do not even mention PPIs. The only exception is the Italian Guideline [372], which clearly states that the routine use of PPIs is not recommended in patients with acute AP. This guideline and the former Japanese one [373], suggest that these drugs might be considered *on a case-to-case basis*, provided specific indications, such as NSAID use, peptic ulcer disease or bleeding, occur.

Chronic pancreatitis (CP) is a progressive, irreversible, fibro-inflammatory disease of the pancreas, in which the pancreatic secretory parenchyma is damaged and replaced by fibrous tissue, resulting in morphologic changes of the ducts and parenchyma. This process eventually culminates in permanent impairment of exocrine and endocrine function of the pancreas. The clinical manifestations of CP include abdominal pain as well as steatorrhea, weight loss, and malnutrition, all resulting from the loss of adequate enzyme and bicarbonate secretion [374, 375], and the so-called *pancreatogenic* diabetes, arising from loss of β-cell function [376, 377].

Chronic disabling pain, which poses a major detriment to the quality of life, is present in nearly 80% to 90% of patients with CP. Although two meta-analyses found no real benefit of enzyme replacement therapy (ERT) [378], the role of pancreatic enzymes in mitigating abdominal pain still remains unclear and some experts recommend a 6-week trial of non enteric-coated pancreatic enzymes [379].

Together with pain, most patients with advanced CP will develop at some point pancreatic insufficiency, secondary to loss of pancreatic parenchyma. Pancreatic lipase secretion is lost faster than other secretions. It is well known that steatorrhea (due to decreased luminal hydrolysis of dietary fat) develops only when the lipase levels drop to less than 10% [380]. However, this does not minimize the importance of amylase and trypsin, which should be integral part of pancreatic enzyme supplementation. Traditionally, ERT is indicated in patients with steatorrhea (fecal fat greater than 15 g/d) and weight loss [381]. Supplemental pancreatic enzymes alleviate diarrhoea and maldigestion, associated with pancreatic exocrine insufficiency and also aid in

maintaining normal nutrition, thus improving the quality of life [381].

Pancreatic enzymes in tablet form are susceptible to inactivation by stomach acid, therefore limiting their activity in the duodenum. The secretion of bicarbonate, which maintains an alkaline pancreatic juice, is dramatically reduced in most patients [381]. In addition, during the post-prandial period, the pH of the stomach and the upper small intestine is significantly decreased [382]. When postprandial pH in the small intestine becomes 4 or lower, bile acids precipitate and digestive enzymes (lipase in particular) lose their activities. Strategies to circumvent this include administering higher amounts of pancreatic enzymes and increasing gastric pH with the use of a PPI.

The favourable effects of antisecretory drugs on abolishing steatorrhea are primarily caused by reducing acid and volume of secretion. The end results of these actions are to elevate the pH in the stomach and duodenum, and facilitate the delivery and concentration of lipase in the duodenum. Another important effect is, however, the reduction of duodenal volume flow, which in turn increases the concentration of intraduodenal lipolytic activity [383]. Enteric-coated formulations protect pancreatic enzymes from the low pH in the stomach, allowing enzymes to maintain their potency when they reach the duodenum. Enteric-coated enzymes are then released in the duodenum, where pH exceed 5.5 units. Despite these formulations being resistant to breakdown by gastric acid, some studies have shown improvements in fat absorption when they are administered with concurrent acid suppression therapy [381].

The use of PPIs is recommended by International guidelines for CP or/and pancreatic exocrine insufficiency [384-392]. The Italian guidelines [385] state clearly that addition of PPIs is recommended *only* in patients with refractory steatorrhea and that acid suppression is not indicated in patients with an adequate response to ERT. These recommendations encompass the main diseases associated with exocrine pancreatic insufficiency (like acute pancreatitis, chronic pancreatitis, pancreatic cancer, cystic fibrosis, celiac disease, IBD, etc.), defined as an inadequate pancreatic enzyme activity to digest food, generally

due to either insufficient enzyme production, insufficient enzyme activation, or to early enzyme degradation [387, 393].

5.3.14 Safety Concerns with Long-Term Proton Pump Inhibitors Therapy

Summary of the current evidence**:** *Being very effective and considered very safe, PPIs are often prescribed inappropriately, especially in the elderly. The tolerability of PPIs is generally good, with an adverse event rate of 1–3%. Some adverse effects are plausible and predictable. Others are idiosyncratic, unpredictable, and rare. Overall, the benefits of PPI treatment outweigh the potential risks in most patients, who have a relevant and appropriate indication.*

Although overuse and misuse may challenge the safety profile, the tolerability of PPIs has been remarkably good. Adverse reactions generally occur at a rate of 1–3%, without any significant differences among PPIs. Untoward effects most commonly include headaches, nausea, abdominal pain, constipation, flatulence, diarrhea, rash, and dizziness. Long-term studies indicate a tolerability profile similar to that found in short-term trials [22-25].

PPI-related adverse events involve the GI tract as well as other organs and systems. The majority of these events have been summarized in comprehensive reviews, to which the reader is referred [394-400]. The potential risks of long-term PPI therapy, along with the respective evidence summary, are outlined in **Table 5.3.1** and in **Table 5.3.2**.

Gastric pH is relevant for the absorption of several drugs and its modification by antisecretory therapy may significantly modify their pharmacokinetics [401]. PPIs also influence drug absorption and metabolism by interacting with adenosine triphosphate-dependent P-glycoprotein (e.g. inhibiting digoxin efflux) or with the cytochrome P450

(CYP) enzyme system (e.g. decreasing simvastatin metabolism), thereby affecting both intestinal first-pass metabolism and hepatic clearance. A number of studies have shown that omeprazole (and, to a lesser extent, lansoprazole) carries a considerable potential for DDIs, since it has a high affinity for CYP2C19 and a somewhat lower affinity for CYP3A4. In contrast, pantoprazole and rabeprazole display a lower potential for DDIs [402, 403]. DDIs therefore represent a molecule-related effect rather than a class-effect [404].

These interactions are clinically relevant mostly for drugs with a narrow therapeutic index (e.g. diazepam, warfarin, antipsycothics, etc.) [402, 405]. In addition, PPIs metabolism is very rapid in most Caucasian subjects (extensive metabolizers), so that their half-life ranges from only 0.5 to 2.1 hours [405]. Indeed, the prevalence of poor metabolizers, potentially at increased risk of drug interactions, is as low as 1.2 3.8% in Europe as compared to 23% in Asia [406]. This could explain why only few of the reported DDIs involving PPIs have been shown to be of clinical significance.

Recent studies have raised concerns about a possible adverse interaction between clopidogrel and PPIs (currently prescribed to patients, who are receiving dual antiplatelet therapy to prevent upper GI bleeding) that could reduce the antithrombotic effect of the former and, therefore, lessen protection against CV events in high-risk patients. However, current evidence shows that - while concomitant use of *some* PPIs with clopidogrel does attenuate the antiplatelet effect of clopidogrel – this effect is likely to be not clinically relevant [277, 279, 407, 408]. Conversely, denying PPIs to patients at GI risk would result in increased life-threatening GI bleeding [278, 409, 410].

PPIs are among the most widely used prescription drugs. Although alarms have been raised about their long-term safety, the preponderance of the evidence does not strongly support the concerns, publicized over the last few years and the benefit to risk ratio remain favourable. Some adverse effects are plausible and predictable. Others are idiosyncratic, unpredictable, and rare.

The best available information on long-term safety of PPIs derives from the SOPRAN [74]

and LOTUS [73] trials, comparing anti-reflux surgery with omeprazole or esomeprazole, respectively. Safety data were collected from patients during the 12-year period of the SOPRAN study (n = 298) and the 5-year period of the LOTUS study (n = 514). Reported serious adverse events and changes in laboratory variables were analyzed. Across both studies, serious adverse events were reported at a similar frequency in the PPI and ARS treatment groups. Laboratory results, including routine hematology and tests for liver enzymes, electrolytes, vitamin D, vitamin B_{12}, folate and homocysteine, showed no clinically relevant changes over time. The only expected difference concerned gastrin and chromogranin A levels, which were elevated in the PPI group, with the greatest increases observed in the first year [411]. Despite a continued proliferative drive on enterochromaffin-like cells (ECL) during esomeprazole treatment, no dysplastic or neoplastic lesions were found [412]

Based on the quality of the overall evidence, the benefits of PPI treatment outweigh the potential risks in most patients, especially if PPI use is based on a relevant and appropriate indication [6, 44]. On the contrary, patients treated without an appropriate therapeutic indication are *only* exposed to potential risks. Because PPIs are *overprescribed* in many patients, in particular for continued long-term use, the clinical effects should always be reviewed and justified attempts should be made to stop any therapy that may not be needed [398].

Table 5.3.1 Concerns about long-term therapy with proton pump inhibitors (PPIs): Digestive System.

Theoretical Concern	Evidence Summary
Consequences of long-term PPI-induced hypergastrinemia	PPI-induced hypergastrinemia is enhanced in *H. pylori* infected patients [413], where the antisecretory effect is increased
	No controlled human data support the increased risk of gastric cancer [92, 414]
	More and higher quality studies are needed to confirm or refute any causal link with gastric cancer [415, 416]
	No data support the increased risk of CRC [417, 418]
	An increased frequency of fundic gland (inflammatory) polyps has been reported [416, 418]
	Rebound acid hypersecretion (with consequent increased frequency of acid-related symptoms) is of uncertain clinical relevance [83]
	Despite unclear biological mechanism(s), two large observational studies [419, 420] reported conflicting results concerning the putative risk of pancreatic carcinoma in PPI users
Infectious consequences of long-term PPI-induced hypochlorhydria	Growing evidence suggests that acid suppression increases the risk of enteric infections by *C. difficile* [421, 422] and other pathogens [421, 423, 424]
	Increased *Candida* infections in the mouth, esophagus, stomach, and upper small intestine of PPI users has been documented[425]
	PPI users are at increased risk of SIBO [426], while cirrhotic patients, taking these drugs, are at higher risk of spontaneous bacterial peritonitis [355, 356]
Non-infectious consequences of long-term PPI-induced hypochlorhydria	According to a single case control study [427] exposure to antisecretory drugs, including PPIs, was associated with a increased of subsequent diagnosis of coeliac disease, but the underlying mechanism(s) are unclear
Dysbiosis	Dysbiosis, probably represents the most consistent adverse effect of PPIs, responsible - besides of enteric infections and SIBO - for gas-related symptoms as well as aggravation of NSAID-enteropathy [428, 429]
Consequences of long-term PPI-induced hypochlorhydria on electrolyte and nutrient absorption	No consistent effects on calcium or iron absorption have been reported [395, 396]
	Severe symptomatic hyponatremia has been reported as a consequence of SIADH [430]
	Data support an increased risk of developing significant B_{12} deficiency [431], but this is a clinical concern only in elderly or malnourished patients
Idiosyncratic reactions to PPIs	Magnesium intestinal transport is inhibited by PPIs and may lead to rare but potentially life-threatening hypo-magnesiemia [432, 433]
	Lansoprazole-induced microscopic colitis has been described [434], with complete resolution after drug discontinuation. However, recent data suggest a class effect [435]
	Despite some case reports, epidemiological studies showing an association between PPI intake and acute pancreatitis have given conflicting results [44]

Table 5.3.2 Concerns about long-term therapy with proton pump inhibitors (PPIs): Extra-digestive effects.

Theoretical Concern	Evidence Summary
Infectious consequences of long-term PPI-induced hypochlorhydria	More and higher quality studies are needed to confirm or refute any causal link with CAP, especially in long term users [436, 437]
Bone consequences of long-term PPI therapy	PPI use is not associated with accelerated BMD loss or osteoporosis [438], which are thought to be the underlying biological explanation for the *modest* increase in the risk of bone fracture [439-441]
Dementia and Alzheimer's Disease	Although, in a mouse model, very high-dose PPI use increased the level of β-amyloid in the brain [442], human data linking these drugs to development of dementia are conflicting [443, 444]
	The risk of development of Alzheimer's Disease in PPI users appears comparable to that of any incident dementia [445]
Delirium	PPIs were found to be an independent factor associated with development of delirium in geriatric inpatients [446], likely reflecting poly-pharmacy and DDIs
Acute Myocardial Infarction (AMI)	Since PPIs do not impair endothelial function [447], more and higher quality studies, which have to be free from confounders [448], are needed to confirm [449, 450] or refute [278, 279, 409] any causal link with AMI
Idiosyncratic reactions to PPIs	PPIs appear to be the most common cause of drug-induced AIN. After PPI withdrawal and corticosteroid therapy, almost all patients recovered a normal renal function [451, 452]
	There is a small but definite increase in risk of CKD in long-term PPI users, likely resultaing from undiagnosed or residual PPI-induced AIN [452]
	Polymyositis and other myopathies, including the life-threatening condition of rhabdomyolysis, have been described with all PPIs [453, 454]
	Immediate and delayed hypersensitivity to PPIs, with cross reactivity amongst the members of the class, has been described [455]
PPI-drug interactions	Acid suppression reduces absorption of levothyroxine, ketoconazole, itraconazole, atazanavir, cefpodoxime, enoxacin and dipyridamole while increasing that of nifedipine, digoxin and alendronate [401]
	Concomitant use of some PPIs with clopidogrel attenuates the antiplatelet effect of clopidogrel, but may not be clinically relevant since there are no clinical differences in the risk for major adverse CV events [402, 404]
	Only a few drug interactions (e.g. with diazepam, warfarin, phenytoin and methotrexate) involving PPIs (mainly omeprazole and lansoprazole) are of clinical significance [402, 404]
	DDIs may be more frequent in some patient populations (e.g. AIDS or cancer)[404]
	The degree of DDIs associated with PPIs and the respective clinical outcomes depend on different factors such as genotype status of CYP enzymes, ethnicity and drug regimen [404, 406]

5.4 Discussion

PPIs remain the leading evidence-based therapy for acid-related diseases, including GERD, PU disease, dyspepsia, NSAID-induced ulcer, *Helicobacter pylori* infection, and hypersecretory disorders such as Zollinger-Ellison syndrome [1, 3, 4, 456, 457].

The strong evidence supporting PPI efficacy and a favourable safety profile has led to overuse of these drugs in many treatment arenas [11]. Surprisingly, despite more than 25 years of extensive literature, addressing PPI therapy in upper GI disorders, inappropriate use remains consistently high both in the hospital and in primary care [7]. In a recent US study [458], only 39% inpatients' prescriptions were compliant to guidelines, with a difference between academic and non-academic hospitals (compliance being 50% *versus* 29%, respectively). Prophylaxis of upper GI bleeding in low risk patients was the most common indication for non-compliant prescriptions while that of guideline compliant prescriptions was treatment of dyspepsia [458].

The questionable and inappropriate PPI use in the absence of documented evidence, supporting clear indications, is likely due to the perception that many physicians have about PPI safety, which makes them forgetting to assess risks and benefits of (especially long-term) therapy [459]. Several studies [*for review see* [11] have shown that physicians frequently do not review and document PPI indications, which often results in their long-term or even indefinite continuation.

There are two main concerns pertaining to PPI overuse and misuse: drug expenditure, which has risen dramatically in recent years, even after the introduction of cheaper generic formulations [460], and growing safety concerns [394-400, 461]. Despite their concentration within the secretory canaliculi of the parietal cell and their pharmacologic selectivity [462], also PPIs have a "dark side" [463]. Sir William Osler once famously commented that *no drug has a single effect* and these secondary actions range from mildly inconvenient to frankly dangerous [464]. PPIs are no exception.

Non-judicious PPI use is a matter of great concern in the elderly, who often have multiple comorbidities, are taking multiple medications, and hence at increased risk of

long-term PPI-related adverse outcomes. PPI-related adverse events involve the GI tract as well as other organs and systems. The potential risks of long-term PPI therapy, along with the respective evidence summary, have been summarized in the **Safety section**. While some concerns about the possible adverse effects of PPIs (including an increased risk of gastric carcinoids, gastric carcinoma, decreased absorption of minerals and vitamins) have been raised since their introduction in the late 1980s, more recently the number of publications dealing with PPI-related adverse outcomes has steadily increased [394-399, 461]. It is worth mentioning, however, that the majority of studies are observational in nature and do not allow for establishing causality, but merely associations [465]. Residual bias is always a concern in observational studies, even after statistical adjustment, because all confounding factors cannot be recorded or even be known. When effect sizes are small (relative risk/odds ratio/hazard ratio <2), it is not possible to determine whether the association is valid or represents the result of residual bias [466]. Hazard ratios for PPI use and some reported adverse effects (e.g. dementia, CKD, any fracture or CAP) were all ≤1.5. Nevertheless, if a true casualty exists, even small effect sizes can result in a meaningful risk for common interventions and conditions.

Despite PPIs carrying - like any other classes of drugs - some risks, they should not be denied to patients who are likely to benefit from them merely because of concerns about *putative* adverse effects. There is generally some equivalence between the acceptable burden of adverse effects and the severity of the illness being treated [464]. However, patients with acid-related diseases are often otherwise 'healthy' subjects, who take drugs for a given condition. What level of undesirable effects would be acceptable for them and who will bear the cost of treating any ensuing iatrogenic disease? A number of simple and potentially effective preventive measures should be recommended for some (if not all) safety concerns in order to minimize them.

First of all, PPI therapy should be evidence-based. Decisions on whether or not to initiate or continue PPI therapy should be sound and PPIs should only be prescribed when there

is an appropriate clinical indication. Clinical guidelines can certainly help. In this Position Paper, we have reviewed the current available guidelines, together with the systematic reviews and meta-analyses used to generate them, and synthesized the knowledge in a number of statements (i.e. **Summary of the current evidence**) and in ***Table 5.4.1***.

Table 5.4.1 Current indications of proton pump inhibitor (PPI) therapy.

Clinical setting	PPI dose and duration
GERD	
Erosive Esophagitis (A/B)	Standard dose PPI therapy for 8-12 weeks
Erosive Esophagitis (C/D)	Double dose PPI therapy for 8-12 weeks
NERD	Standard dose PPI therapy for 4-8 weeks
Long-term Management (both GERD and NERD)	Standard (or half) dose PPI maintenance (continuous, intermittent or on-demand, depending on clinical characteristics of the patient)
Barrett's Esophagus	Long-term individually-tailored PPI therapy
Extra-digestive GERD	Standard or double-dose PPI therapy for at least 12 weeks
Eosinophilic Esophagitis	Standard or double dose PPI therapy for 8-12 weeks
H. pylori Eradication	Double dose, twice daily, PPI therapy for 7-14 days (in combination with antimicrobials)
Non *H. pylori*-related PU disease	Standard dose PPI therapy for 4-8 weeks
Zollinger-Ellison Syndrome	High-dose (eventually twice daily) long-term PPI therapy
Stress Ulcer Prophylaxis in patients with risk factors	Standard PPI therapy by intravenous route only during ICU stay
Dyspepsia	
Uninvestigated Dyspepsia in Patients Younger than 45 Years	Standard or half-dose empiric PPI therapy for 4 weeks
Functional Dyspepsia (EPS phenotype)	Standard or half dose PPI therapy for 4-8 weeks
NSAID-gastropathy	
Prevention of gastro-duodenal lesions and events	Standard or half-dose PPI therapy, starting form the very first dose of NSAID in patients at GI risk
Treatment of gastro-duodenal lesions	Standard or half-dose PPI therapy, starting form the very first dose of NSAID in patients at GI risk
Steroid therapy	No need for gastroprotection unless used in combination with NSAIDs
Anti-Platelet Therapy	Standard dose PPI therapy, starting form the very first dose of antiplatelet agent in patients at GI risk
Anti-Coagulant Therapy	No need for gastroprotection unless used in combination with antiplatelet therapy
PU Bleeding	Intravenous bolus of 80 mg of the available injectable PPIs, followed by 8 mg/h for 72 hours
Cirrhosis	
Hypertensive gastropathy	No need for acid suppression
Prevention or/and treatment of esophageal ulcers after sclerotherapy or variceal band ligation	Standard dose PPI therapy for 10 days (longer treatment should be avoided taking into account the risk of spontaneous bacterial peritonitis)
Pancreatic Diseases	
Acute pancreatitis	No benefits from acid suppression
Chronic pancreatitis	Standard PPI therapy only in patients with steatorrhea, refractory to enzyme replacement therapy

Guidelines rely on both evidence and expert opinion; they are neither infallible nor a substitute for clinical judgment. They do, however, go beyond systematic reviews to recommend what should and should not be done in specific clinical circumstances. Despite guidelines being developed to improve quality of care received by patients, they have been criticized for recommending too little or too much and even for providing reasons for NHS or insurances payers to deny coverage [467]. Guidelines are often inflexible and can actually harm by leaving insufficient room for clinicians to tailor care to individual patient circumstances and medical history. What is best for patients overall, as recommended by guidelines, may be inappropriate for individuals [468]. Only evidence-based recommendations, which consider the balance between benefits and risks, and weigh these considerations using patient (rather than expert and societal) value, should be followed in everyday clinical practice. Taking these considerations into account, we have tried to distill the current evidence and provide physicians with clear *patient-oriented* recommendations, beyond cost and reimbursement issues. Medicine is a rapidly evolving field, however, and the validity of guidelines will not necessarily stand the test of time: indeed, today's assumptions may no longer be valid tomorrow. Health care providers should therefore stay tuned and constantly update their knowledge.

PPIs continue to be prescribed outside treatment guidelines. In Europe, the most common inappropriate use of PPI is for the prevention of gastric damage in co-therapy with agents, which have a low gastrotoxicity, if any, or in patients without GI risk factors for significant gastro-duodenal damage [30, 31, 469-471] as well as in the prevention of stress-induced bleeding [14, 472-474]. PPIs are often started as an inpatient treatment and continued (often long-term) on discharge for non-indicated reasons [14, 475, 476].

PPIs are now available – *at half the prescription dose* – as over-the-counter (OTC), i.e. they can be purchased directly without prescription. Although the proportion of patients taking OTC PPIs internationally is unknown, it may well represent the majority of use globally. A recent US survey [477] found that 32% of patients with GERD symptoms were using OTC PPIs, with only 39% of consumers using them optimally, with better symptom

relief. Besides patients, also 50% of US gastroenterogists use (i.e. suggest to patients) OTC PPIs [478]. Despite the vast majority of them (76%) felt that OTC brand name and generic formulations were equally effective (which is not always the case [479]), the majority of them recommended the brand medication [478].

The availability of OTC PPIs provides consumers with options other than antacids and H_2RAs for self-medication of acid-related symptoms. Prospective clinical trials have shown the efficacy of these drugs, taken on demand or intermittently on GERD management, with potential for cost reduction [17]. Although guidelines for OTC use [18, 480] suggest a short course (2 week treatment) of PPIs in patients with typical complaints (acid and/or regurgitation), and *without alarm symptoms*, great potential for misuse and/or overuse does exist. Major concerns include management of patients in whom symptom persist despite acid suppression, appropriate administration and the potential masking for more serious pathology, like malignancy. Therefore, guidelines and position statements are not just for specialists and GPs but should be extended to clinical and community pharmacists and patients alike.

PPIs are among the safest class of drugs. Although concerns have been raised on their long-term safety, the preponderance of evidence does not strongly support the concerns, publicized over the last few years, and the absolute risk is probably low. Some adverse effects are plausible and predictable. Others are idiosyncratic, unpredictable, and rare. Based on the quality of the existing evidence, the benefits of PPI treatment outweigh the potential risks in most patients, especially if PPI use is based on a relevant and appropriate indication [6, 44]. Conversely, patients treated without an appropriate therapeutic indication are *only* exposed to potential risks and the benefit-to-risk ratio becomes very low. Consequently, the overall focus should be on the appropriateness of PPI therapy and on a regular assessment of the need for continued PPI treatment.

Nearly all the adverse outcomes associated with PPIs occur among patients who receive *long-term* therapy; minimizing the duration of treatment by periodically reviewing a patient's need for acid-suppressive therapy could eliminate or substantially reduce the

risk of adverse outcomes. Therefore, during continued long-term use, the clinical effects should always be reviewed and attempts be made to stop any therapy that may not be needed [398]. It is imperative to use the lowest dose of drug required to achieve the desired therapeutic goals. This may entail implementing discontinuation of treatment in asymptomatic patients as well as step-down [481, 482], intermittent [481, 483, 484] or on-demand PPI therapy [484-486] for maintenance of GERD. It should be emphasized, however, that PPI treatment in GERD is merely palliative in nature, since it does not address the underlying pathophysiology, something only ARS is able to achieve [487-489]. Therefore, in young fit patients, needing continuous acid suppression, fundoplication should be considered. Intermittent or on-demand PPI therapy is not suitable for NSAID users, since the risk of serious GI events is constant in those patients with GI risk factors and can persist for some time after stopping therapy [170, 222].

Under the current situation of PPI misuse, opportunities do exist do to increase appropriateness in order to enhance effectiveness and safety of drug therapy as well as minimize overall healthcare costs. As always, education is the key [7, 490]. Issuing guidelines and implementing them represent the most rational approach to problem. Judicious surveillance of hospital use and prescription refills in the outpatient settings [460], with re-evaluation and justification for continued treatment, can minimize the potential for adverse effects and achieve cost-saving. However, surveillance must be close and continuous since the benefits attained could be short-lasting. Indeed, in a recent Canadian study [491], deprescribing guidelines were associated with a decline in PPI use during the initial 6 months, but prescription patterns began to climb back to baseline afterwards.

Overall, PPIs are irreplaceable drugs in the management of acid-related diseases. However, PPI treatment – as any kind of drug therapy - is not without risk of adverse effects. The overall benefits of therapy and improvement in quality of life significantly outweigh potential risks in most patients, but those without clear clinical indication are only exposed to the risks of PPI prescription. Sticking with evidence-based guidelines represent the only rational approach to an effective and safe PPI therapy.

5.5 Acknowledgements

We are indebted to Professor Richard H Hunt (McMaster University, Hamilton, ON, CA) and Professor Jean Paul Galmiche (University of Nantes, France) for the critical reading of the manuscript and the very useful suggestions. We are also very grateful to all the National and International Experts (listed below), who kindly agreed to review the various statements of the Position Paper, contributing to the improvement of both contents and wording.

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6 Comparing Tapentadol to Oxycodone/Naloxone Combination: Building Castles in the Air

Pain is a normal human experience, but some people are hardwired physically, emotionally or both to progress to chronic pain states. Epidemiological studies suggest that around 20% of adults in Europe experience chronic pain[1] and that its severity correlates with a reduction in physical and mental health. Severe chronic pain, in particular, presents a considerable burden for patients and can have a considerable impact on their quality of life, with a direct correlation to symptoms, such as anxiety, depression, and limited social functioning.[1, 2] Despite an effective pain management is considered as a fundamental human right,[3]more than one-third of these individuals feel that their pain is inadequately managed and are dissatisfied with their treatment.[1]

Opioids are routinely prescribed for treatment of chronic pain. In the past two decades, there has been a massive increase in the number of opioid prescriptions, prescribed daily opioid doses and overall opioid availability. Treating chronic pain with opioids went from being largely discouraged to being included in standards of care[4] and titrating doses until patient's self-report adequate control has become common practice.[5] Intersecting with the upward trajectory in opioid use are the increasing trends in opioid related adverse effects, especially prescription drug abuse, addiction and overdose deaths. And indeed, despite limited evidence and variable development methods, recent guidelines on chronic pain agree on several opioid risk mitigation strategies, including upper dosing thresholds, cautions with certain medications, attention to drug-drug and drug-disease interactions and use of risk assessment tools.[6]

Despite the skilled use of opioid analgesics, the effective and safe treatment of chronic pain still remains an unmet clinical need and there is a strong demand for new drugs and new regimens.[7] Novel opioids and/or opioid combinations have been marketed in the recent years, including tapentadol and oxycodone/naloxone. Tapentadol is the first

US FDA-approved centrally acting analgesic having both μ-opioid receptor agonist and noradrenaline reuptake inhibitory activity with minimal serotonin reuptake inhibition. This dual mode of action may make tapentadol particularly useful in the treatment of neuropathic pain. Its low affinity toward the μ-opioid receptors should lead to a reduction in gastrointestinal adverse effects, namely nausea, vomiting and constipation.[8] Constipation, experienced by some 40% of patients, is particularly challenging and – together with the other gastrointestinal symptoms - may actually dissuade patients from using the required analgesic dose to achieve effective pain relief.[9] The rationale of oxycodone/naloxone combination (both compounds included in an oral extended-release formulation in a 2:1 fixed dose ratio) represents a new approach to counteract opioid-induced constipation, while maintaining effective analgesia. Following its release, naloxone acts locally on the gut, antagonizing the inhibitory effect of the opioid on μ-receptors. After being absorbed in parallel with oxycodone, naloxone is rapidly and completely inactivated through a high first-pass effect in the liver.[10, 11]

Being their availability relatively recent, the experience with both medications is limited and these two approaches toward a better pain management have not yet *directly* compared. Drs Coluzzi and Ruggeri[12] should be therefore commended for their attempt to provide clinicians with an, albeit indirect, comparison of tapentadol extended release (ER) formulation and oxycodone/naloxone controlled release (CR) combination. The Authors performed a meta-analysis and an economic evaluation of these two therapeutic strategies for the treatment of musculoskeletal pain through an indirect comparison with CR oxycodone. There are, however, several methodological and clinical issues that may affect the findings of the study and limit their validity and clinical relevance. Let us to examine and comment each of these issues.

Firstly, the authors compared *indirectly* tapentadol ER and oxycodone/naloxone CR in the absence of head to head randomized control trial (RCT). Indirect comparisons make

important assumptions about the stability of relative treatment effects across RCTs. Indeed, RCTs might be done in different populations, with different concomitant treatments, different overall management of disease, and, last but not least, different outcomes. Coluzzi & Ruggeri[12] included three RCTs that compared oxycodone/naloxone CR *versus* oxycodone CR. The first study[13] enrolled patients with a documented history of moderate to severe chronic non-malignant lower back pain adequately managed by an opioid analgesic, and the aim was to demonstrate the superiority of oxycodone/naloxone CR formulation over placebo with respect to analgesic efficacy. This study also included an active group (*i.e.* patients treated with oxycodone CR) to compare the analgesic efficacy and the impact on bowel function of oxycodone/naloxone CR compared to oxycodone CR. The other two trials[14, 15] were carried our in patients with moderate-to-severe non-cancer pain that required continued around-the-clock opioid therapy and who suffered of constipation induced or aggravated opioid therapy. The principal aim of those studies was to evaluate the efficacy of oxycodone/naloxone CR compared to oxycodone CR in relieving constipation. On the contrary, all the trials,[16-18] evaluating tapentadol ER in opioid-naïve patients and included in the analysis of Coluzzi & Ruggeri,[12] had as principal aim the assessment of the efficacy and safety of this new medication compared to oxycodone CR. Therefore, it is questionable using data coming from studies whose aims are clearly heterogeneous.

Secondly, how a clinical indirect comparison should be performed? Certainly, not putting "apples and oranges" together.[19] Indeed, a fundamental principle of the meta-analytic technique is analysing data from homogenous populations with the very same outcome. As a consequence, the approach followed by the Authors is not a straightforward one. One simple method is to compare the results of individual arms from different studies as if they were from the same RCT. An example of this approach is presented in **Table.6.1**. Evaluating the four variables selected from the studies that Coluzzi & Ruggeri[12] included in their analysis, it appears that oxycodone/naloxone CR has a significantly better profile than tapentadol ER. Nevertheless, this kind of

unadjusted indirect comparison has been criticized for discarding the within trial comparison, increasing liability to bias and over-precise estimates.[20] A more robust methodological approach is to carry out an adjusted comparison using the so-called "network meta-analysis", which takes into account the inferences about the relative merits of the treatments that have never been compared.[21, 22]

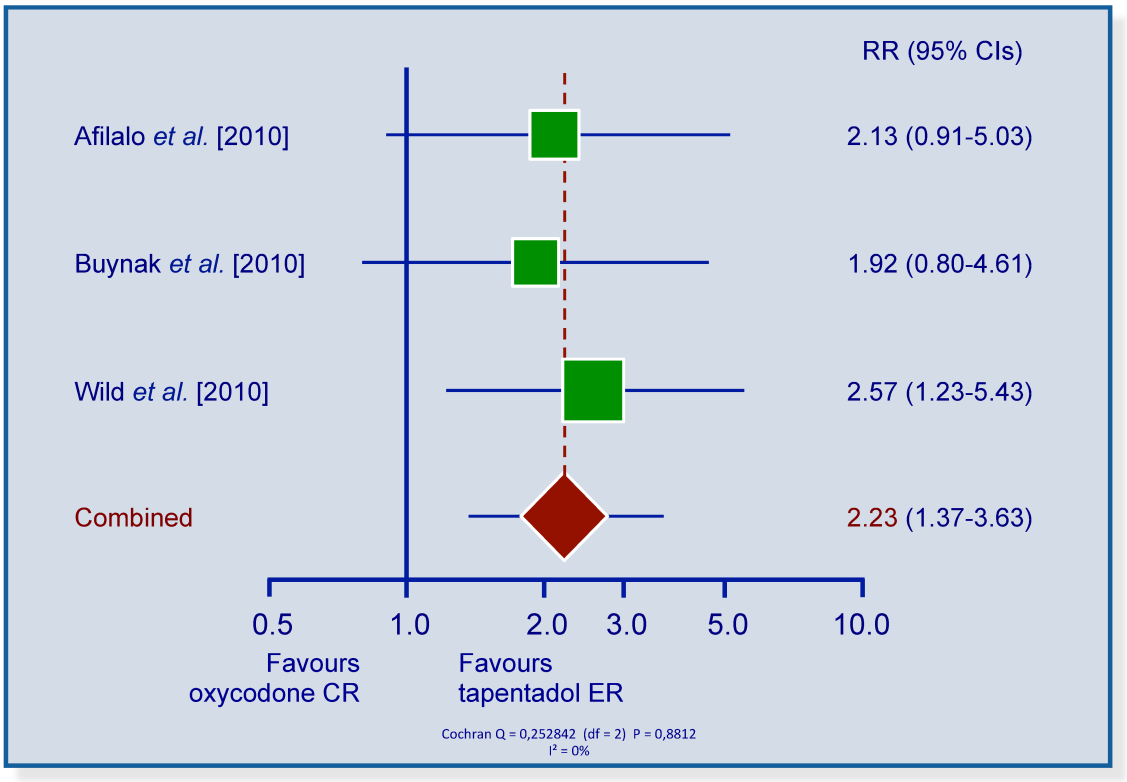
Table.6.1 Unadjusted comparison between tapentadol ER and Oxycodone/Naloxone CR (Oxy/Nal).

Variables	Tapentadol ER % (95% CI)	Oxy/Nal % (95% CI)	Difference % (95% CI)	p value
Overall AEs	81.4% (79.4 to 83.3)	59.1%* (53.1 to 64.9)	22.2% (16.3 to 28.3)	<0.0001
Overall W	51.1% (48.6 to 53.6)	13.0% (10.2 to 16.4)	38.1 (33.9 to 41.9)	<0.0001
W to AEs	20.2% (18.2 to 22.3)	4.7% (2.9 to 7.1)	15.5% (12.5 to 18.2)	<0.0001
W to LoE	6.4% (5.2 to 7.7)	2.0% (0.9 to 3.7)	4.4% (2.3 to 6.0)	<0.0001

*Data available in only 2 out of 3 studies[13, 15]
AEs, adverse events; W, withdrawn; LoE, lack of efficacy
Adverse events and post-randomization withdrawal rates were taken from each study.[13-18]
Proportions, their differences, and 95% confidence intervals (CIs) were calculated using the method recommended by Newcombe and Altman[23]

Thirdly, one of the statements of the Markov model proposed by Coluzzi & Ruggeri[12] is called "discontinuation". Authors likely refers to discontinuation due to adverse events, since they presented the results for this variable in their meta-analysis However, even if the Authors took into account the variable "discontinuation due to lack of efficacy", it is not clear if they considered that variable in term of efficacy. In the trials evaluating tapendatol ER *versus* oxycodone CR,[16-18] the risk ratio (RR) of discontinuing the treatment due to lack of efficacy was significantly greater for tapendatol ER (**Figure 5.51**). Since, in pharmacovigilance, drug failure is considered a type F adverse event,[24] this increased likelihood of ineffectiveness of tapentadol should translate also into a worse side effect profile.

Figure 5.51 Meta-analysis of discontinuation due to lack of efficacy in trials comparing tapentadol ER and oxycodone CR.



Data were pooled by using a random effects model to give a conservative estimate of the 95% confidence intervals. [25]

Fourthly, Authors analysed the *incidence* of constipation during treatment. This is correct for the RCTs evaluating tapentadol ER,[16-18] but might be debatable for two of the trials[14, 15] evaluating oxycodone/naloxone CR. As already emphasized, the aim of those trials was to evaluate the efficacy of oxycodone/naloxone CR compared to oxycodone CR in relieving opioid-induced constipation, assessed using the Bowel Function Index (BFI). Both studies showed a significant improvement of BFI, and therefore, the data regarding constipation presented in the Forest Plot (Figure 5 of the Coluzzi & Ruggeri's

paper[12]) do not reflect the aim of the studies, and – when included in an economical model - will produce ambiguous findings.

Lastly, Authors considered among the adverse events (AEs) those related to the gastrointestinal system (GIS), to the central nervous system (CNS) and to the skin, as stated in Figure 1 of their article.[12] However, data on AEs concerning the skin are not presented or discussed. Furthermore, it is not clear why they decided to consider the GIS and CNS AEs separately instead of just considered the "overall" number of AEs observed during the study for each treatment.

In summary, although commendable, the paper of Coluzzi & Ruggeri[12] fails to reach the aim of the study, *i.e.* to provide clinicians with an objective evaluation of the clinical and economic impact of tapentadol ER, in comparison with oxycodone/naloxone CR, in patients with muscoloskeletal pain. Indeed, their conclusion that tapentadol ER is more cost-effective is not supported by a critical evaluation of the available literature. Only a large, well designed clinical trial "affording" a direct head to head comparison between these two medications will allow a real comparison of their cost-effectiveness. For now, taking these conclusions into account when making therapeutic choices would be like building castles in the air, whose crash will undoubtedly have disastrous consequences. A dispassionate look at the current data will doubtless lead the reader to agree with our viewpoint.

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7 Conclusions

In this thesis, we evaluated three different gastroenterological cases. In the first, the use of the systematic review and meta-analysis was used to assess if a specific treatment (namely rifaximin) was effective and safe to treat a disease (namely SIBO). Our results[1] showed that rifaximin was able to eradicate the infection in more than two-thirds of patients. There was a significant heterogeneity, which means that this finding cannot be considered very robust. There could be several reasons for heterogeneity: difference in type of patients enrolled (e.g. ethnicity, socio-economic status, etc.), difference in severity of diseases among patients in each trial and between trials, difference in awareness of disease (some studies were performed almost 20 years ago, when SIBO was really little known even among specialists), different test used to diagnose the infection, etc. It might be objected that we combined apples and oranges (i.e. different kinds of studies) in the same analysis. However, it should be stressed that one of the strength of meta-analysis is that these differences, if identified, can be investigated formally[2]. And indeed, using the meta-regression technique, we were able to explore several possible factors potentially responsible for heterogeneity, founding that the type of design of the study (i.e. RCT vs. observational), dosage of rifaximin, and use of medication that could affect the gut microbiota were potentially associated with an increase in eradication rate. Nevertheless, one important finding of this study was that part of the heterogeneity was due to the lack of shared protocols, or better, guidelines that Authors could follow (e.g. if a GHBT is used, that a certain cut-off must to be used, and the test have to last a certain amount of time, etc.) Data on adverse effect were also collected. However, these data suffered from all the limitations that we described in Chapter 4 of this thesis. The cross-sectional prevalence of the AEs was very modest but, as we stated before, the absence of evidence is not the evidence of absence in this field. Therefore, we would like to recommend for future trials dedicated tool for reporting adverse events in order to improve their assessment.

In the second manuscript, the evidence-based approach was used to review the current literature on PPI use and develop a position paper addressing the benefits and potential harms of acid suppression with the purpose of providing evidence-based guidelines on the appropriate use of these medications[3]. The introduction of PPIs into clinical practice has revolutionized the management of acid-related diseases. However, data form studies in primary care and emergency settings suggest that PPIs are frequently prescribed for inappropriate indications or for indications where their use offers little benefit. It took almost two years of intense work to develop the recommendation published, covering a wide range of diseases where PPIs could find an indication. Some peculiarity of this work need to be highlighted. Firstly, this paper represents a joint position of three important societies: Italian Society of Pharmacology (SIF), the Italian Association of Hospital Gastroenterologists (AIGO) and Italian Association of General Practitioners (FIMMG). For this reason, the statements presented take into account pharmacological and clinical features as well as the point of view of General Practitioners. Secondly, we asked, for each topic assessed, a well-recognised national and international specialist their evaluation, in order to improve quality and strength of the current evidence. Thirdly, a specific section was devoted the possible harm of this medication. PPIs are at the moment irreplaceable drugs in the management of acid-related diseases. Nevertheless, PPI– as any kind of drug – is not without risk of adverse effects. The overall benefits of therapy and improvement in quality of life significantly outweigh potential risks in most patients, but those without clear clinical indication are only exposed to the risks of PPI prescription. Adhering to evidence-based guidelines represents the only rational approach to an effective and safe PPI therapy.

Finally, since National Health Systems are currently collapsing, pharmacoeconomic analysis represents an integral part of the decision process. However, the evaluation of economic impact of a given treatment is inevitably based on the quality and robustness of the systematic reviews and meta-analysis. In this connection, we showed [4] that the conclusions of an article concerning tapentadol ER - in comparison with oxycodone/naloxone CR - were misleading. Indeed, with a coherent methodological and

meta-analytic approach we were able to show that the comparisons made by the Authors were incorrect and actually reached an opposed conclusion.

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