November 3, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5247-review.doc).

Title: ROLE OF CHEMOPROPHYLAXIS WITH EITHER NSAIDS OR STATINS IN PATIENTS WITH BARRETT ESOPHAGUS.

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2. Dr Isaacs revised English language

3. Revision has been made according to the suggestions of the reviewer

a) Population and observational studies presented in tables 1 and 2, while study results were summarized in the text. b) Epidemiological data presented before mechanisms of action and comments were introduced in the mechanism section to connect epidemiological data with mechanisms of action. c) Abstract was rewritten. d) The following paragraph was introduced in the "introduction" to comment on risk factors for adenocarcinoma. If individuals at high risk of neoplastic progression can be more accurately distinguished from those who are likely to follow a benign course (risk stratification), using host and lifestyle factors combined with validated markers of risk from serum and esophageal tissue, then substantial improvement in clinical management of BE could be achieved. Clinical and demographic factors that have shown some promise in being predictive of malignant transformation in BE are male gender [10,11], increasing age [11], length of Barrett's segment [12-14], duration of BE [13], and size of hiatal hernia [14]. There is little evidence to suggest that total alcohol consumption, or specific alcoholic beverages, modifies risk of EAC in the general population [15,16], while smoking [16-19] and obesity [16,20] raises the risk for neoplastic progression. e) The following paragrapg was introduced in "future directions" Because mortality due to cardiovascular disease is high in BE patients, "technical review on the management of Barrett's Esophagus today" suggests screening for cardiovascular factors in BE patients and aspirin and statin use as warranted [45]. Because we have shown no benefit for non-aspirin NSAID use in BE patients with ischemic heart disease [53] and substantial cardiovascular side effects are expected [103,104], use of non-aspirin NSAIDs should be withhold in patients with BE and cardiovascular co-morbidities, at least until more clinical data might justify their use. f) Acronyms index was

introduced g) Discussion on general advantages and disadvantages of observational studies was eliminated. h) the following paragraph as introduced discussing cardiovascular side effects of NSAIDs I) We speculated that adjustment for obesity and smoking could reduced the protective effect of statins. Also we introduced the following sentence Because adiponectin and ghrelin can interfere in vitro with EAC cell apoptosis [126], obesity, a parameter overlooked by most observational studies [40,41,43], mandates father attention.

(2) a nd b) Epidemiological data presented before mechanisms of action and comments were introduced in the mechanism section to connect epidemiological data with mechanisms of action. c) The following section was introduced on NOX-5 mechanism of action Reactive oxygen species may damage DNA, RNA, lipids, and proteins, leading to increased mutation and altered functions of enzymes and proteins (*e.g.* activation of oncogene products and/or inhibition of tumor suppressor proteins). They also related to cellular immunity, signal transduction and modification of extracellular matrix. Low levels of reactive oxygen species are produced in non-phagocytic cells and are thought to be by-products of aerobic metabolism [59]. Pulsed acid treatment and bile significantly increases H_2O_2 production in BE cells via NADPH oxydase NOX-5-S over-expression. It also increases calcium ion influx and cyclic amp reactive element binding protein [60,61]. Increased cellular calcium ion influx causes up-regulation of NADPH oxidase NOX5-S [62]. Overproduction of reactive oxygen species derived from up-regulation of NADPH oxydase NOX5-S, as well as H_2O_2 overproduction can up-regulated NF KB [63], and as a result leads in COX-2 over-expression [64]. d) Population and observational studies presented in tables 1 and 2, while study results were summarized in the text. e) The following part was introduced to justify why we wanted this study Although cancer surveillance is performed in most institutions, once diagnosis of BE is rendered, the true cost-benefit ratio of this endeavour is still essentially unknown [22]. Surveillance does not interfere with the neoplastic process and could not affect the pre-neoplastic stem cell population generated in the bone marrow. Thus there is quest for global and more interventional strategies. Chemoprevention represents one of the most attractive ways to reduce the incidence of EAC, especially in the high-risk group of BE individuals, since it can affect the neoplastic process from its early beginning. Moreover, because it could be effective even under insufficient gastric acid suppression [23], it is superior to BE ablative techniques that presuppose adequate acid suppression to prevent BE recurrence [24]. Finally, since BE surveillance cost-effectiveness has been undermined by recent data suggesting a low risk of malignant transformation [25,26] and BE ablation is too expensive [27],

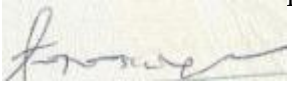
chemoprevention seems to represent an attractive alternative [28]. At present there are no proven chemo-preventive agents, although non-steroidal anti-inflammatory drugs (NSAIDs) and statins appear to offer the most attractive combination of risks and benefits.

The aim of this review is to assess current experimental and epidemiological evidence and evaluate whether or not NSAIDs and statins may reduce the risk of developing EAC. Moreover we aim to clarify how existing findings could be included in the EAC aetiological models, as well as any side effects that would follow clinical application of NSAIDs and statins for cancer prevention.

(3) There were no more comments apart from English revision

4. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Pharmacology and Therapeutics*.



Sincerely yours,

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