CANADIAN ASSOCIATION OF GASTROENTEROLOGY
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May 15, 2006

Mr. Denis Bélanger, B.Sc.Phm
Manager, Best Practices Recommendations
COMPUS & CCOHTA
600-865 Carling Avenue
Ottawa, ON K1S 5S8

Re: Canadian Association of Gastroenterology Feedback on the March 6th COMPUS Summary of Findings on Proton Pump Inhibitors – Interim Report, Dyspepsia

Dear Mr. Bélanger,

I am pleased to provide comments (appended to this letter) from the Canadian Association of Gastroenterology (CAG) in regards to the COMPUS interim report on the *Summary of Findings on Proton Pump Inhibitors*, specifically regarding the Dyspepsia portion of your report.

Most all of the general comments (our letter dated April 17th 2006, http://www.cag-acg.org/mediaroom/government.htm) have been echoed by the specialists providing a review of the Dyspepsia portion of your report. I will therefore not repeat our overall concerns with the COMPUS process and documentation.

I have attached a listing of the comments from two reviewers (experts in the field of dyspepsia), specifically regarding the dyspepsia portion of your document.

Regards,

Paul Sinclair
Executive Director, CAG

GENERAL COMMENTS ON THE DYSPEPSIA SECTION:

- This review is very confused and the validity of the paper is highly dubious. The authors appear to have confused the issues (i.e. mixing statements on the evidence on GERD with dyspepsia, and unclear regarding reference to strategies), the evidence cited is incorrect (GERD trials are cited to support uninvestigated dyspepsia), out-of-date, and hence the conclusions and guidelines are not very helpful. There needs to be clarification of exactly what the authors are trying to discuss.

- The first section of the COMPUS report dealt with GERD. This current section should deal with dyspepsia however it repeatedly includes GERD, both as guidelines and statements, and for evidence cited. It is unclear if the authors understand the area and the result is a fatal flaw that makes this whole section questionable, and in need of complete revision. Some clarity could be had by considering the *H. pylori* negative section separately, and not part of test & treat.

- Dyspepsia is not clearly defined. In particular, this is important to mention for the NSAID section. Here, there are recent papers that clearly support PPI (very recent esomeprazole paper).

- The references provided are out-of-date in that the most current and the most important ones are not included, i.e. CanDys 2005, AGA, ACG. In some instances, the evidence provided has nothing to do with the statement.

- The data has been incorrectly interpreted in some instances (e.g. PPI and antacids, PPI and functional dyspepsia). There would appear to be a negative bias against PPI therapy and this, even in the face of clear evidence – this creates a sense of non-credibility surrounding this document.

- The document puts a lot of weight onto the PRODIGY and the Quebec CRUM – two things that were our experts in the field of dyspepsia were not familiar with. This document should emphasize the CanDys (Canada National Group) and AGA and ACG (North American) literature. The CADET studies (Hp, and HN – are again key Canadian data, directly relevant to this document, and the strongest data available (however they have not been referenced at all). More use of economic evaluations is critical. There must also be a discussion that one cannot make global recommendations given that the prevalence of *H. pylori* changes with race etc, and therefore one has to consider treatment on individual basis.

COMMENTS ON THE DOCUMENT GLOSSARY:

- Alarm features are independent of primary care, or not
- H2RA and PPI should be spelled out the first time
- Asymptomatic ulcer: they specify peptic ulcer disease but should be more generic, i.e. any ulcer that is asymptomatic
- Continuous medical therapy definition should not be limited to GERD treatment
- Dyspepsia definition is good as it uses the CanDys definition, but it should also include reflux-like dyspepsia, i.e. should lump the subtypes of symptom complex first then functional (non-ulcer) dyspepsia. There is no need to have two separate terms, rather they are equal. The term 'uncomplicated dyspepsia' - suggest delete that one as it is never used.
- Empirical therapy is simply treatment based on symptoms without investigations, the qualification about basing on treatment without adequate data to support its use is not needed nor accurate
- ENRD should also have NERD: non-erosive reflux disease. Consider removing the term symptomatic GERD – incorrect and no longer used.
- Functional dyspepsia should not include a time frame
- *H. pylori* also causes MALT lymphoma
- Intermittent treatment of GERD: should be relapse of a patient's previous symptoms or condition.
- Non-ulcer dyspepsia definition should not say insignificant, should say normal endoscopy
- On-demand should include the concept that this is patient driven.
- Quadruple therapy, agree with the definition, however it is used more generically to imply any four drug combination
- If they're going to have a definition for esophagitis and reflux esophagitis, suggest the latter should say acidic gastric contents
- Symptomatic ulcer - again should be generic about ulcers, not peptic ulcer disease
- Ulcer bleeding, should not mention enlarging ulcer – irrelevant

DETAILED COMMENTS ON THE DYSPEPSIA SECTION:

- How is recommendation D1D and D1E different?
- D1D, D1E, D1F are uninvestigated GERD comments, not dyspepsia. Having said that this endorses that GERD symptoms are part of the dyspepsia definition, but this needs to be clearly noted.
- Question D2: not strictly test & treat here, really is *H. pylori* positive, eradicate vs. if *H. pylori* negative, then treat empirically with an acid suppressive agent
- D2 is thus a bit out of place in this section
- D3 important to define dyspepsia in this NSAID area as many studies didn't use a typical definition of dyspepsia
- D4A Disagree. Moayyedi *et al* meta-analysis shows a clear, small benefit
- D4D is a non-evidence based statement
- D5 ii: nonsense to put in the *H pylori* eradication dose here. Little evidence to support half dose PPI, what is PRODIGY guideline?
- D1A page 91: It is probably true that there is no evidence to concretely recommend test and eradicate vs. empirical PPI but in areas where the prevalence of *H. pylori* is greater than 20%, economic evaluation shows the test-eradicate strategy is preferred (Ladabaum U, Chey WD, Scheiman JM, Fendrick AM. Reappraisal of non-invasive management strategies for uninvestigated dyspepsia: a cost-minimization analysis. Aliment Pharmacol Ther 2002; 16: 1491–501.) Or if the prevalence of *H. pylori* >12% for NUD (Spiegel BM, Vakil NB, Ofman JJ. Dyspepsia management in primary care: a decision analysis of competing strategies. Gastroenterology 2002;122:1270-1285)
- This section misses important, more recent guidelines:
  - Guidelines for the Management of Dyspepsia. Nicholas J. Talley, M.D., Ph.D., F.A.C.G.,1 Nimish Vakil, M.D., F.A.C.G.,2 and the Practice Parameters Committee of the American College of Gastroenterology. (Am J Gastroenterol 2005;100:2324–2337)
  - American Gastroenterological Association Technical Review on the Evaluation of Dyspepsia. Talley, Vakil, Moayyedi. GASTROENTEROLOGY 2005;129:1756–1780
  - Veldhuyzen van zanten SJ, Bradette M, Chiba N, Armstrong D, Barkun A, Flook N, Thomson A, Bursey F. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: An update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. Can J Gastroenterol 2005;19:285-303.
  - Reference 126, Talley is outdated.
- Page 93: D1B section. All three references provide clear support that a PPI is more effective than alginates and antacids, yet the conclusion is that the evidence is not in agreement. How can this conclusion be possible? When this document ignores the obvious, the reader should be skeptical to accept any of its recommendations.

- Page 95 section D1D completely incorrectly interprets the CanDys recommendation. The COMPUS document fails to understand the population it is referring to. The CanDys recommendation and data support the use of PPI in GERD. The section they need to concentrate on, in relation to this COMPUS Dyspepsia section, is the *H. pylori* negative dyspepsia group. The COMPUS group should cite the 2005 CanDys review and the CADET-HN study as the single strongest RCT evidence in this area.

- The cited Venables and Galmiche studies are GERD trials, not uninvestigated dyspepsia trials.

- D1E, D1F, D1G, D1H as already stated do not belong here; they belong in the GERD section.

- D2A: Test and treat needs to be better explained. The test and treat strategy technically should be test all patients, and if positive, eradicate. If negative, then treat empirically. In practice, a treatment management study like this has not been done. The best evidence comes from the CADET-HP study (test for Hp and if positive eradicate) and the CADET-HN study (Test for Hp and if negative give empiric therapy) [note these are not listed as evidence]. From a practical perspective the test and treat really means, test and if positive eradicate.

- Evidence not cited include the updated CanDys guidelines (2005), the CHSG guidelines, NICE and the 2005 AGA and ACG guidelines.

- D2A evidence, Delaney has nothing to do with the strategy. In fact all the evidence they give really is a strategy of test and treat vs. Prompt endoscopy, NOT empiric treatment. Therefore the whole section is fatally flawed.

- D2B: again the NICE guidelines and the Scottish guidelines suggest that one can extend over the age of 55. There is support from CADET-HN and PE trials that did include older patient, without adverse outcomes.

- D2D, D2E should be considered separately from Test and treat. CADET-HN is strongest evidence by far.

- D3A, D3B. PPI and dyspepsia in NSAIDs. This section is outdated. There are two recent RCTs that support this for PPI - a recent literature review is needed. At the very least they should cite the Can Dys guidelines from 2000/2005 – at least evidence based and more up to date than the reference (45) used.

- D4A: Laine MA is long outdated! The Moayyedi Cochrane review is current and shows a definite but small benefit.

- D4B again the best evidence is recent Cochrane review.

- D4D pertains to assertion that empiric acid suppression should not be continued however the cited evidence does not address this. The recommendation should be changed to state that in the patient that responds to acid suppression, there is no reason to discontinue treatment. Recommend dropping this altogether. D4E is similar and more pertinent.

- D5A there is no comparative dyspepsia trial that compared all the PPI's.

- D5B: Far too much evidence is cited from these PRODIGY guidelines which are not accepted or endorsed guidelines. You really should be using the CanDys, AGA and the ACG guidelines for these North American opinions and supplement this rigorous international guidelines (NICE and Scottish).

- On page 87, question D1, i: As first-line therapy, there is a synopsis of existing recommendations D1A. The third sentence states "early endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment". This is at odds with the Bytzer study (Lancet 1994;343:811-6) which is alluded to in reference #126 (Aliment Pharmacol Ther 1999;13:1135-48, specifically page 1138).

- Furthermore on page 87, there is a "Synopsis of Existing Recommendations" including D1E, D1F and D1G which allude to patients with dyspepsia when symptoms "mimic those of GERD". Should these recommendations not truly be in the section on GERD if they are not are any there?

- On page 89, question D5 section ii there is a recommendation quoting the PRODIGY guideline but this guideline has neither been clearly referenced, or discussed?

- On page 90, Synopsis of Existing Recommendations D1A, the guidelines/consensus is listed and the year and page number are given. However, getting the page number appears rather peculiar. Furthermore, with the NICE guideline, page 84 is listed and this page does not exist (the guideline is 47 pages long). With respect to the guideline on that same page by Nick Talley, there is a list of "four major strategies for the management of dyspepsia" but this is not really a guideline.

- Also on the bottom of page 90, in the section on supporting evidence, there is a comment on two good quality RCTs, but the numbers are way too small to claim equivalence.

- On page 91, there is a study quoted from the British Journal of General Practice which unfortunately is a very obscure reference for which I could not obtain full text. In the table under intervention, empirical treatment is given as "ome 20 mg". Should provide a standard set of abbreviations for these medications.

- On page 95, there is section D1D on Supporting Evidence which quotes the Venables study from 1997 but the study really is a GERD study and doesn't support conclusions regarding uninvestigated dyspepsia. This problem with using GERD studies extends to D1E Guideline Statements on page 98 where the Synopsis of Existing Recommendations D1E talks about symptoms which "mimic those of GERD" and then uses supporting evidence on pages 98 and 99 which are clearly just reflux studies. Unclear what these statements are doing in a section on uninvestigated dyspepsia. There is no information regarding D1F on page 100 and - why we bother discussing this issue without data. On page 101, there is a comment under Supporting Evidence for D1G which talks about one good quality RCT, but this study that is quoted as being good quality was not blinded. Furthermore, the paper by Kaplan-Machlis et al discussed on the top of page 102 is said to talk about second line therapy but the patients were only taking two weeks or more of OTC therapy in this study was totally a hard current study in any event.

- With respect to D1H also on page 102, we really have no data. The same can be said for D2B guidelines on page 106.

- With respect to D2C, page 107, there is a discussion of the Delaney systematic review to support non-age based test and treat but there's no specific discussion in a systematic review about age.

Furthermore, in the paper (Chiba et al, 2002), there is the caveat in the discussion that the authors note a recommendation of caution in applying the strategy over the age of 50. I think it is difficult to apply recommendations for a test and treat strategy and individuals over the age of 50 or 55 if the only discussion is around efficacy and lack of reported problems. If someone were to have new onset of dyspepsia beyond the age 50 or 55, many gastroenterologists would not be comfortable in employing a test and treat strategy for the concern of missing the occasional patient with neoplasia.

- On page 110, there are no data for D2E. Not sure why there is not a comment that we can make any reasonable recommendations to the same can be said for D3A on page 111.

- Also on page 111, there is a discussion about the role of PPIs for NSAID-induced dyspepsia with section ii discussing high-risk patients. There needs to be a definition given for a high-risk patient somewhere in the document.

- On page 113 there is a Synopsis of Existing Recommendations D4A at the top of the page which lists "for proven functional dyspepsia…" Hard to ever rule out functional dyspepsia entirely but we can certainly exclude organic disease.

- On page 114, question D4, does this really deal with the role of PPIs or isn't really about acid suppression since the papers referenced talk about acid suppression. The questions regarding the role of PPI's for functional dyspepsia go on and on through pages 114 to 119. I am not entirely sure why there are several different sections with very similar discussion but different papers are presented. Can this information not be consolidated? On page 120, D4E Guideline Statements also seem to be based on no data. The same can be said for D5B.

- Typographical and other errors

    - On page 92 at the bottom of the page, D1B Supporting Evidence gives a summary which states that the data indicates that PPIs are more effective than antacids/alginates at reducing dyspeptic symptoms (for global assessment, and heartburn, but not epis̲gastric pain). This should obviously read "epigastric pain". The same error is made at the bottom of page 93 D1C. There also needs be a space there under the have the section for "In theRCTs… which should read "In the RCTs…" On page 94 under D1D: Guideline Statements the statement is made that PPIs or H2 RAs or prokinetics for up to four weeks *is* recommended in this should clearly read *are* recommended. On page 101, the table for D1G: Supporting Evidence lists a column title called "Intervention" but the column is too narrow, so we have "Interventio" on one line and the "n" on the next line.