

December 18th 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format

Title: Doctor Communication Quality and Friends' Attitudes Influence Complementary Medicine Use in Inflammatory Bowel Disease

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Name of Journal: *World Journal of Gastroenterology*

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Our Sincere appreciation for allowing us the opportunity to resubmit this manuscript for consideration of publication in the esteemed World Journal of Gastroenterology. We feel that the manuscript has been substantially improved after incorporation of reviewer and editor suggestions, which were constructive.

I wish to advise manuscript changes based on the following reviewer comments:

Reviewer 1:

In this study, the authors examined the frequency of regular CAM use in three Australian cohorts of contrasting care setting and geography, and identified independent attitudinal and psychological predictors of CAM use across all cohorts. The aim and the messages are clear, the design was well organized, and the number of subjects is large enough. This information is quite useful for the readers of The Journal. There are few questions to be addressed.

1. *The authors found “covert conventional medication dose reduction” as a significant factor associated with the CAM use. However, as the authors pointed out, the causality relationship between them is not clear and an intriguing subject. This may also be confounded by the efficacy of conventional medication. These may be discussed more in detail.*

We agree that the association between covert dose reduction (CDR) of conventional IBD medication and CAM use for IBD is very interesting, and that it is a new finding in this cohort of subjects. This has now been published in Journal of Crohn's and Colitis as a separate manuscript reporting this phenomenon of patient induced dose reduction of conventional medication without the knowledge of the IBD physician for

the first time. At the time of manuscript submission of the current CAM study to WJG, this CDR manuscript was not yet accepted and thus was not available to reference. Whilst the focus of this current CAM manuscript is different, there is overlap with this landmark CDR paper as an association was demonstrated between CAM use and CDR. Formal path analysis would be required to definitively attribute causality to CAM use as the causative factor in CDR behaviour, and in the future we plan to investigate this further. It seems likely that both CDR and the decision to use CAM are driven by similar patient health beliefs and desires (ie belief in efficacy of conventional medication thus continuing to take doses, but desire to limit adverse effects thus dose reducing and using CAM to “value add”) This theory of patient reasoning and behaviour is not yet proven and will be further explored in future works. The place in the literature for the current CAM paper is that of reporting these associated phenomena and to introduce these concepts to the IBD community as a spring board for further study, as well as to focus more on other newly found independent predictors of CAM use such as the influence of social contacts and communication within the patient doctor relationship.

The following paragraph in the discussion has been added / modified, and should be complementary to the discussion within the JCC published manuscript regarding CDR, which is now available in the public arena. We apologise that this was not available to help put these findings into context at the time of initial review, and understand why this intriguing issue appeared only briefly addressed.

“Previously reported predictors including covert dose reduction of conventional medications, the seeking of psychological treatments, adverse effects of medications and increased QOL were confirmed in this study. Free text responses strongly suggested that IBD CAM users tend to reduce rather than omit doses of conventional medications on the assumption that CAM use will provide a “medication sparing” effect, the aim being to minimise adverse effects of conventional medications¹. This newly described phenomenon is the subject of a separate publication, which suggests that similar underlying health beliefs and desires drive both CAM uptake and CDR behaviour. Although abundant free text data from this study support this hypothesis, formal path analysis has yet to be undertaken to confirm the direction of causality in the association between CAM use and CDR.”

Interestingly, a study of another chronic disease, hypertension, also found an association between deliberate under dosing of conventional medication and CAM use², and this supports our new finding in the IBD population, amongst whom this phenomenon has not been previously investigated.

2. *The report of “Mountifield, et al. 2014” should be referred in the References section, if accepted for publication.*

Thank you, this paper has now been published as above and is now referenced appropriately.

3. *In the discussion section, the discussion on the most significant finding (such as the newly found factor for CAM use) should better to come to the first of the section.*

The order of the discussion has been reworked in response to this sensible suggestion, to start with the new CAM predictors then progress to previously established ones in order to present novel information first then establish that our findings are generalizable as other populations have other predictors in common. We feel the discussion is more interesting, informative and coherent as a result, and thank the reviewer for this input.

The opening paragraph in the discussion has been re-ordered to reflect newly described factors as a priority as follows:

“This study demonstrates the high frequency of CAM use amongst IBD patients in Australia, and suggests that such use occurs independently of health care setting and geography. Newly identified attitudinal and psychological risk factors include dissatisfaction with patient-doctor communication, CAM use by social contacts and fewer depressive symptoms. We confirm both the known demographic risk factors for CAM use and known behavioural associations such as covert dose reduction, psychotherapeutic support seeking, and adverse effects of conventional medications.”

Reviewer 2:

- A) *There are several different kinds of CAM as the authors show, and the purpose of them are also different from each other. However, the analysis is done as CAM being a single therapy. The authors should make more detailed analysis and add some comments on that point to reach a better conclusion.*

This is an excellent point and one which we tried to consider in the original analysis. It was not possible to statistically analyse the associations of attitudes with particular CAM types as the majority of subjects (64.5%) reported using more than one CAM type, often overlapping both physical and homeopathic methods. This may reflect real life practices in CAM use³ and is an important finding in itself. This meant that it was not possible to determine or statistically analyse attitudes towards and behaviours associated with different CAM types. We agree this is important for the reader to understand and this was not previously clear from the manuscript.

This sentence has been added to the results section:

“The regular use of more than one CAM type (ie physical as well as homeopathic methods) was reported by 64.5% of subjects.”

This is an important point raised by reviewers and is now emphasised early in the discussion as follows:

“The frequency of regular CAM use was slightly higher in our study population (45.4%) than reported previously in Australia⁴, but within the range reported internationally⁴⁻⁶. Similarly to the Italian study assessing regional variation in CAM use⁷, we found no difference in overall rates of CAM use between cohorts, but did not find regional variation in the type of CAM chosen either. Some variation in choice of CAM type is seen between populations globally, our predominantly Caucasian cohorts being comparable with New Zealand IBD subjects amongst whom herbs and vitamins were most commonly used⁸. Interestingly nearly two thirds of subjects used more than one type of CAM, however, overlapping physical and homeopathic methods and rendering further analysis by CAM type difficult. “

The limitation paragraph now reads:

“Statistical analysis differentiating by CAM type is likely to be important but was not feasible in this study as most subjects (64.5%) reported using more than one therapy type.”

We have also clarified the CAM type table (Table 2) to inform that the CAM distribution mentioned was defined by the type mentioned first by each subject in response to this free text question. “Primary CAM type” is now the header for this table. We acknowledge this was unclear previously and thank the reviewer for bringing this to our attention

This is a methodologic problem in many studies of CAM use. We acknowledge the difficulty in defining CAM use, and note that a recent review of efficacy of IBD CAM therapies excluded dietary supplements and manipulative therapies in their definition of CAM⁹.

This important point is now added to the limitation section accordingly:

“Also, the definition of CAM is not uniform across studies and in this case was defined as what subjects felt was outside of “conventional” therapy.” This definition has been used by other investigators also¹⁰.

B) The degree of disease activity and response to conventional therapy is different among patients, which could greatly affect the use of CAM. The author should add some analyses or comments on that point.

We acknowledge the potential influence of disease activity and response to conventional therapy on CAM uptake. Unfortunately it was beyond the scope of this questionnaire based study relying on self report to assess disease activity accurately enough to analyse this statistically. We agree that this may be important and feel that it must be emphasised as a significant limitation of the study and a suggestion to improve the design of future similar works.

We do have data regarding subjects' reasons for CAM uptake, however, and report in the results section that a small but important minority of CAM users started therapy due to inefficacy of conventional medications as follows:

"A smaller proportion (14.4%) cited lack of efficacy of conventional medications in treating IBD."

The following has been added in the limitation section of the discussion:

"The limitations of this study include the small amount of clinical information obtainable from subjects by self-report, including disease activity and response to conventional therapy, and these may influence CAM decisions."

Reviewer 3:

The manuscript titled "Doctor Communication Quality and Friends' Attitudes Influence Complementary Medicine Use in Inflammatory Bowel Disease" reports predictors of complementary medicine use among UC patients, physician attention to communication and the patient-doctor relationship. The topic seems laudable regarding UC. The manuscript was also written well. Tables should be improved and the reference style should be in accordance with the journal guideline.

This input is appreciated, and tables and reference style have both been modified as requested, with the authors' apologies.

Reviewer 4:

The authors have conducted a study to examine the use of alternate medicines in IBD patients. While the study is interesting, the discussion is too long and needs to be shortened.

The following sections in the discussion have been deleted, and this has improved the readability of the manuscript:

"A greater proportion of our study subjects using CAM (52.5%) felt it was effective for their IBD than in other studies¹¹. Almost 1 in 5 subjects (16.7%) ceased their conventional medications, however, and this is comparable with Korean¹² and Spanish data¹¹. "

"Cited reasons for CAM use were comparable with other data, although only 14.4% of our subjects cited lack of efficacy of conventional IBD medications, compared with 40% in a similar study⁶. Interestingly, lack of efficacy was not statistically associated with CAM use in our study."

"Our findings support previous data identifying younger age, female gender and permanent higher educational or employment level as predictors of CAM use, whilst disease type was not associated⁸. After adjustment for demographic factors, a trend was observed suggesting non-smokers were more likely to use CAM than current smokers. This has not been previously reported, but may be consistent with the desire for a health conscious lifestyle previously associated with CAM¹³."

“The vast majority (94%) of CAM users in this study offered free text responses regarding CAM views, suggesting a willingness to engage in discussion with conventional health practitioners on this issue. The theme amongst free text responses in this study was a desire for more “natural” therapies, highlighting a common perception that natural is synonymous with safe, despite some evidence to the contrary¹⁴.”

Other shorter sections and sentences have also been deleted or truncated.

The total word count for the manuscript is approximately 2940 words (substantially less than at first submission).

In response to other queries, I (Dr Reme Mountifield) as first author am a native English speaker and as such have not used external language services. With regard to the services of a professional biostatistician, methods were not reviewed externally. The biostatistical analysis was performed by Dr Reme Mountifield and Dr Antonina Mikocka Walus, both authors on the manuscript with extensive experience in this kind of analysis.

Please note this study is not a randomised controlled trial nor a clinical trial but an observational study, and thus has no clinical trial registration documentation applicable. It has been fully Ethics approved by our Institutional Board as stated in the manuscript, and informed consent obtained from all subjects. Please inform us if further documents are required to support this observational study and we can provide them immediately.

We kindly thank all editors and reviewers for their constructive input and hope that subsequent changes to the manuscript meet with your approval.

Kind regards,

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