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Adhesiolysis: A reanalysis of the AHRQ Report on Chronic Pelvic Pain

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1 Abstract and Citation

Adhesiolysis: A reanalysis of the AHRQ Report on Chronic Pelvic Pain
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www.synechion.com/IAS2012-AHRQAdhesiolysis.pdf

Background: In 2009, over 430,000 in-patient adhesiolysis procedures were performed in the USA to cut adhesions, abnormal connections between organs in the body, often to treat chronic pelvic pain (CPP). In a recent report commissioned by the Agency for Healthcare Research and Quality (AHRQ) on therapies for CPP in women, an assessment of the effectiveness of adhesiolysis for CPP relied on one study (Swank) which concluded that although laparoscopic adhesiolysis relieves chronic abdominal pain, it could not be recommended to treat chronic abdominal pain because it was not more beneficial than laparoscopy alone.

Purpose: To critically review the Swank study and AHRQ report on CPP regarding their analysis and conclusions on the effectiveness of adhesiolysis for CPP.

Method: The Swank study and AHRQ reports were subjected to critical review regarding the topic of adhesiolysis. The lead authors of both were contacted by telephone or email to clarify certain aspects of their research.

Results: A number of statistical and methodological flaws including a randomization bias, a Type II error and failure to consider the effect of reformation, challenge the validity of the conclusions made by Swank et al. In addition to relying on the Swank study without considering these flaws, it is suggested that the AHRQ report has improperly applied its selection and grading criteria.
The initiative of AHRQ is welcomed in compiling a much-needed report and raising the level of awareness about CPP, its treatment and the need for more research. Although the Swank study constitutes an important contribution to the medical literature its inclusion in a forum for the formulation of health policy is premature and possibly detrimental.

Despite some tempering statements within the body of the report the overwhelming impression conveyed by its various summaries and ancillary documents is that adhesiolysis does not benefit noncyclic CPP and that it should not be performed. By inaccurately portraying the effectiveness of adhesiolysis for CPP, the report may have significant and adverse consequences for CPP patients. Left as is, this report and its related documents may be relied upon by payers and other policy makers to deprive, without just cause, many thousands of patients of an avenue of relief of not only adhesiolysis but diagnostic laparoscopy which also appears to provide some benefit.

Conclusion: The following statement is proposed to more accurately reflect what is known about adhesiolysis: *"The relationship between adhesions and pain is very complex. The few studies that address whether or not adhesiolysis benefits patients with CPP are limited either by size, design or interpretation, but nonetheless suggest that in some patients adhesiolysis may provide benefit above that apparently provided by diagnostic laparoscopy alone."*

Clearly, more research is required and non-surgical alternatives for the treatment of CPP should be used where possible. Indeed, this author has recently founded a company whose aim is to commercialize such non-surgical alternatives for many of the procedures discussed in the AHRQ report. In the meantime however, it is important that a full range of treatment options remain available for patients suffering with CPP.

The above arguments have been presented through email discussion with the lead author of the AHRQ report, Dr. Jeff Andrews, who has agreed to revise the report at the next opportunity subject to the availability of funding by AHRQ, which at the time of writing, has been reduced.

2 Executive Summary

2.1 Adhesiolysis

Adhesiolysis is a surgical procedure in which adhesions, abnormal connections that have formed between organs in the body, are cut often in an effort to treat chronic pelvic pain. Adhesions are a leading cause of bowel obstruction and infertility. Although many patients with otherwise unexplained pelvic or abdominal pain have adhesions, the relationship between pain and adhesions is poorly understood. Over 430,000 in-patient adhesiolysis procedures were performed in the USA in 2009, conservatively at a cost of close to $5 billion.

2.2 AHRQ report on non-cyclic pelvic pain therapies for women - background

A report, entitled "Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness" was published by the Vanderbilt Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), an agency of the US Department of Health and Human Services. By inaccurately portraying the effectiveness of adhesiolysis for chronic pelvic pain (CPP), the report may have significant and adverse consequences for patients seeking treatment.

Having presented our case to the lead author of the report, he has agreed to make the appropriate amendments to the report in its next revision.

2.3 Overall Impression Given by the Report Regarding Adhesiolysis

The report relied on only one study (Swank et al., 2003) to draw its conclusions regarding the effectiveness of adhesiolysis for chronic pelvic pain. Additionally, it is our opinion that the AHRQ report has improperly applied its selection and grading criteria. The report presents a number of statements about the Swank study that do not accurately reflect its findings, most notably:

- "No evidence of benefit of lysis of adhesions" (page vii)
- "One good-quality RCT evaluated laparoscopic lysis of intraabdominal adhesions and reported no improvement in pain scores over diagnostic laparoscopy." (ES6)
- "Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life." (Slide 17 of CME Powerpoint presentation)

Despite some tempering statements (e.g. p51), the overwhelming impression that one is left with concerning adhesiolysis is that it does not benefit noncyclic CPP, with the implication that it should not be performed. Left as is, this report and its related documents may be relied upon by payers and other policy makers to deprive, without just cause, many thousands of patients of an avenue of relief. A more accurate summary of what is known about adhesiolysis and pain might be contained in the following statement:

"The relationship between adhesions and pain is very complex. The few studies that address whether or not adhesiolysis benefits patients with CPP are limited either by size, design or interpretation, but nonetheless suggest that in some patients adhesiolysis may provide benefit above that apparently provided by diagnostic laparoscopy alone."

2.4 The Swank Study

The goal of the Swank study was to answer the question of whether or not adhesiolysis benefited patients with abdominal (which includes pelvic) pain. It concluded that although laparoscopic adhesiolysis relieves chronic abdominal pain, it was not more beneficial than diagnostic laparoscopy alone. Laparoscopic adhesiolysis could not be recommended as a treatment for

patients with chronic abdominal pain. Statistical and/or methodological flaws challenge the validity of these conclusions:

- The study may have wrongly concluded that there was no difference between laparoscopy only and adhesiolysis, a Type II or Beta error. The Swank study actually showed that 42% of control patients benefited somewhat from laparoscopy only[1] and 57% benefited with additional adhesiolysis (a *differential* improvement of some 15%).
- Selection of the effect size of 35% for the sample size calculation may have been inappropriate.
- Basic assumptions of baseline effect of laparoscopy alone were not met and assumptions of sample size calculation could not be met.
- The study was improperly powered to detect the difference found.
- The study failed to account for adhesion reformation in a realistic determination of effect size. Accounting for a 75% rate of adhesion reformation, as well as the 42% effect of laparoscopy alone could account for the differential improvement of 15% actually observed.
- Swank et al., imply, and the AHRQ report inappropriately concludes that "Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life."
- Sample size calculations were not appropriate to the types of analyses actually performed.
- The study contained a possible bias by its inappropriate pre-randomization treatment of eligible patients. Some reanalyses of data to account for this bias could indicate a positive difference between adhesiolysis and laparoscopy alone.
- The classification by AHRQ of the study as "Good" is challenged on the basis of bias and a possible 20% or greater proportion of patients not meeting the criteria to permit inclusion of this study in the AHRQ report.

2.5 Conclusion: Are we missing the point?

The AHRQ report concluded that both adhesiolysis and laparoscopy relieved pain (equally). Even if the readers of the report conclude that adhesiolysis provides no benefit additional to that of diagnostic laparoscopy, will they recommend that patients undergo diagnostic laparoscopy when other pathology has already been ruled out? Will patients still be offered a diagnostic laparoscopy and the opportunity to be one of 42% of patients who benefits from laparoscopy alone? Patients will likely be offered nothing.

The foregoing analysis is not intended to prove that adhesiolysis is beneficial for treatment of pelvic pain. Given the issues noted regarding the Swank study itself, or its interpretation by the AHRQ report, any conclusion or implication that adhesiolysis does not benefit pelvic pain must be challenged. Clearly more research is needed to clarify this important issue. Above all, the research should at least build on the innovative study designed by Swank and his colleagues and attempt to overcome the shortcomings we have highlighted.

In the meantime let this not be a cause to remove adhesiolysis or even laparoscopy as an option for the treatment of pelvic or abdominal pain, provided other, less invasive measures have been fully explored.

[1] There are a number of biological mechanisms that could account for the effect of what appears to be a "sham" procedure beyond merely that of a "placebo effect." A discussion of these mechanisms is beyond the scope of this paper, other than to say that they may yield important clues about how to treat pain.

3 Report Background

3.1 Adhesiolysis

Adhesiolysis is a surgical procedure in which adhesions, abnormal connections that have formed between organs in the body, are cut by a surgeon. Adhesions themselves can form congenitally, but most commonly as a result of trauma or diseases such as endometriosis, pelvic inflammatory disease or previous surgery, even adhesiolysis. Adhesions are a leading cause of bowel obstruction and infertility. Although many patients with otherwise unexplained pelvic or abdominal pain have adhesions, the relationship between pain and adhesions is poorly understood, partly because of the complex nature of chronic pain itself. Over 430,000 in-patient adhesiolysis procedures were performed in the USA in 2009, conservatively at a cost of close to $5 billion.

3.2 AHRQ report on non-cyclic pelvic pain therapies for women - background

A report, entitled "Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness"[2] was published in January 2012. The report was authored by a team led by Dr. Jeff Andrews, Associate Professor of Obstetrics and Gynecology at the Vanderbilt Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), an agency of the US Department of Health and Human Services. The information in the report, like other AHRQ reports, is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services.

The report applied a number of pre-determined criteria to its evaluation of research appearing in the medical literature concerning pelvic pain and a number of types of treatment, including adhesiolysis. The report was careful to describe not only its conclusions regarding each topic, but also attempted to evaluate the quality of research on which those conclusions were based, in order for the reader to determine the reliability of the conclusions reached by the report.

Accompanying the report on the AHRQ web site are a number of ancillary materials, including a physician summary[3], a patient summary[4], a Powerpoint presentation[5] and a quiz for CME purposes.

In general, we welcome the much-needed report as it has raised the level of awareness about pelvic pain, its treatment and the need for more research. The fact that the report was sponsored by AHRQ, an agency operating under the US Department of Health and Social Services, signifies the importance now attached to this major health and economic problem affecting over 15 million Americans.

However, it is our opinion that by inaccurately portraying the effectiveness of a particular procedure, adhesiolysis, used to treat pelvic pain, the report may have significant and adverse

[2] http://effectivehealthcare.ahrq.gov/ehc/products/195/808/CER41-Pelvic-Pain_20120112.pdf
[3] http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=931
[4] http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1032
[5] www.effectivehealthcare.ahrq.gov/tasks/sites/ehc/assets/file/chronic-pelvic-pain.ppt

consequences for often desperate patients seeking treatment. The basis of our opinion is outlined in this document.

Having presented our case to the lead author of the report through a correspondence which is recorded herein, he has agreed to make the appropriate amendments to the report in its next revision. The purpose of this paper is to summarize the main issues in documentary form.

4 Overall Impression Given by the Report Regarding Adhesiolysis

Although there are a number of reports[6] that adhesiolysis (McClain et al., 2011; Peters et al., 1992; Szomstein et al., 2006) may or may not (Hammond et al., 2004) be of benefit in the treatment of pelvic or abdominal pain, the report relied on only the one study (Swank et al., 2003) meeting its criteria to reach its conclusions regarding the effectiveness of adhesiolysis for pelvic pain. We believe that these conclusions are flawed.

It is important to note that despite our reservations regarding the Swank study, we believe that it constitutes a novel and important contribution to the medical literature about adhesions and chronic pelvic pain. As worthy as the examination of this study is to further scientific inquiry, its inclusion in a forum for the formulation of health policy is premature and possibly detrimental.

In addition to the flaws inherent in the Swank study, it is our opinion that the AHRQ report itself has improperly applied its selection criteria, overestimating its quality. The report presents a number of statements about the Swank study that do not accurately reflect its findings, nor for that matter the report's own categorization of the Strength of Evidence (E7, p53) as "Low." Most notably these statements include:

- "No evidence of benefit of lysis of adhesions" (page vii)
- "One good-quality RCT[7] evaluated laparoscopic lysis of intraabdominal adhesions and reported no improvement in pain scores over diagnostic laparoscopy." (ES6)
- "Aside from the lack of benefit reported for adhesiolysis, (Swank et al.) little evidence demonstrates the effectiveness of surgical approaches" (p71)

There does appear, on page 51 of the 339 page report a more reasonable statement that *"the evidence is insufficient to conclude that surgical intervention is either effective or ineffective for the treatment of CPP."* Despite this and other statements ascribing a "Low" SOE (Strength of Evidence), or the fact the there exists only one "good-quality" RCT (ES6, p53) the overwhelming impression that one is left with concerning adhesiolysis is that it does not benefit noncyclic CPP, with the implication that it should not be performed.

Indeed, in the accompanying Powerpoint presentation used as a CME credit course, the conclusion is even more condensed:

- "Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life." (Slide 17)
- "Among surgical approaches for CPP, both LUNA and laparoscopic adhesiolysis were not found to be superior to diagnostic laparoscopy." (Slide 20)

[6] This is not intended to be an exhaustive review of the subject.
[7] Randomized Clinical Trial

As such, left as is, this report and its related documents, as far as its discussion on adhesiolysis, will be relied upon by payers and other policy makers to deprive many thousands of patients of an avenue of relief, one that may be the only one left after many years of futile search. Some of these concerns have already been expressed by Roman et al. (2009) who in noting that *"the trial should …not have concluded that the two surgical procedures were equivalent.…it is likely that numerous surgeons have abandoned laparoscopic adhesiolysis."*

Indeed, because the report is largely silent on the benefit of laparoscopy alone in 42% of Swank's patients, it may have the effect of depriving patients of diagnostic laparoscopy (i.e. laparoscopy where no procedures are performed other than anesthesia, insufflation, placement of camera and closure) when pathology other than adhesions has already been ruled out. A more accurate summary of what is known about adhesiolysis and pain might be contained in the following statement:

"The relationship between adhesions and pain is very complex. The few studies that address whether or not adhesiolysis benefits patients with CPP are limited either by size, design or interpretation, but nonetheless suggest that in some patients adhesiolysis may provide benefit above that apparently provided by diagnostic laparoscopy alone."

5 The Swank Study

5.1 Summary of the Swank Study

In 2003, Dr. Dingeman Swank and his colleagues from Gouda in the Netherlands published (Swank et al., 2003) the results of a study whose goal was to answer the question of whether or not adhesiolysis benefited patients with abdominal pain. The official abstract of the study is as follows:

> Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet. 2003;361:2250.
> BACKGROUND: Laparoscopic adhesiolysis for chronic abdominal pain is controversial and is not evidence based. We aimed to test our hypothesis that laparoscopic adhesiolysis leads to substantial pain relief and improvement in quality of life in patients with adhesions and chronic abdominal pain.
> METHODS: Patients had diagnostic laparoscopy for chronic abdominal pain attributed to adhesions; other causes for their pain had been excluded. If adhesions were confirmed during diagnostic laparoscopy, patients were randomly assigned either to laparoscopic adhesiolysis or no treatment. Treatment allocation was concealed from patients, and assessors were unaware of patients' treatment and outcome. Pain was assessed for 1 year by visual analogue score (VAS) score (scale 0-100), pain change score, use of analgesics, and quality of life score. Analysis was by intention to treat.
> FINDINGS: Of 116 patients enrolled for diagnostic laparoscopy, 100 were randomly allocated either laparoscopic adhesiolysis (52) or no treatment (48). Both groups reported substantial pain relief and a significantly improved quality of life, but there was no difference between the groups (mean change from baseline of VAS score at 12 months: difference 3 points, p=0.53; 95% CI -7 to 13).
> INTERPRETATION: Although laparoscopic adhesiolysis relieves chronic abdominal pain, it is not more beneficial than diagnostic laparoscopy alone. Therefore, laparoscopic adhesiolysis cannot be recommended as a treatment for adhesions in patients with chronic abdominal pain.

To eliminate any bias patients or those assessing their pain may have had about whether or not adhesiolysis was effective, neither the patients nor those assessing their pain knew whether the patients had received just a diagnostic procedure, or additional adhesiolysis. After 12 months, the researchers concluded that although laparoscopic adhesiolysis relieves chronic abdominal pain, it was not more beneficial than diagnostic laparoscopy alone.

Swank and his colleagues concluded that laparoscopic adhesiolysis could not be recommended as a treatment for adhesions in patients with chronic abdominal pain.

5.2 Type II Error: the study showed no difference vs. the study failed to show a difference

The first problem in the Swank study is that it may have wrongly concluded that there was no difference between laparoscopy only and adhesiolysis, when in fact there may have been. This is called a Type II or Beta error.

Showing no difference is not the same a not being able to show a difference.

The Swank study actually showed that 42% of control patients benefited somewhat from laparoscopy only and 57% benefited with additional adhesiolysis (a *differential* improvement of some 15%).

Can we truly say that there was no difference between the two treatments, or was there really a difference but we just could not detect it? If you were a patient who has endured daily, excruciating abdominal pain for many years, would you forego the chance of being one of the 57/100 patients who improved with adhesiolysis, just to be one of the only 42/100 patients who improved with laparoscopy only?

We need to understand a little about the statistical tests used to answer these sorts of questions.

This study set out to determine whether there was a difference in pain reported by patients after undergoing laparoscopy only, or laparoscopy with adhesiolysis. When designing a study of this kind, certain assumptions must be made in advance about:

- the kind of variability there might be from patient to patient
- the baseline level of pain relief *expected* in the group having only laparoscopy
- the *minimum* difference in % of patients obtaining relief considered to be clinically meaningful (this is called effect size). Note that the bigger the difference, the smaller the number of patients we will need to show that it exists. The smaller this difference, the greater the number of patients we will need to show the difference really exists.

A calculation is then performed (called a sample size calculation) to determine the number of patients needed in the study (called sample size) to demonstrate a difference between the treatments, if one truly exists, with a predetermined degree of confidence (called the power) and a predetermined margin of error (called the significance level).[8]

So in effect the clinical trial is set up to detect a certain predetermined *minimum* difference given our assumptions. If this minimum difference is detected, we say that we detected such a difference. If this minimum difference is not detected, all we can say is that we could not detect this difference. We can't say there is no difference.

But if there really was a difference and we conclude wrongly that there was not a difference, this is called a Type II or Beta error.[9] And that may be exactly what happened here. The Swank study concluded that *"laparoscopic adhesiolysis…was not more beneficial than diagnostic laparoscopy*

[8] For most studies of this type the power and significance level are by convention set at 80% and 5% respectively.
[9] Concluding that there is a difference when there really is not, is called a Type I, or Alpha error.

alone". The difference between the 42% improvement in the laparoscopy group and the 57% improvement in the adhesiolysis group may well have been significant, but we could not detect it because:

- It was of a smaller magnitude than we had expected
- We did not have enough patients in the study to detect that difference

5.3 Was 35% an appropriate effect size to use for the sample size calculation?

In addition to the problem of the Type II error, we must ask whether or not Swank et al. were justified in selecting 35% as their minimally meaningful difference, and why do we care?

There is great debate as to what constitutes a "clinically meaningful effect". Although the AHRQ report (p11) cited published recommendations to set an effect size at 30%, the Swank paper provided no basis for selecting 35% as the effect size. Any discussion I have witnessed or been a part of, for example in regard to FDA approval of anti-adhesion products, has set a minimum as 20%. So selecting a large effect size would make demonstrating that it exists less likely if the other assumptions of the study are not met.

A large effect size is more of a problem because the laparoscopy-only group overperformed

If the assumptions about the study are not met, then our conclusions do not hold water. In this study, although only 25% of the patients in the laparoscopy only group were expected to show some pain relief, 42% actually did. This means that in order to show the expected improvement of 35% with the same sample size, 77% of patients in the adhesiolysis group needed to improve, a much harder goal to achieve. So the study was doomed to failure not because the adhesiolysis group underperformed (57% improvement was pretty close to the 60% level expected), but because the laparoscopy only group overperformed (42% vs. 25%).

So was the actual difference of 57% vs. 42% detected statistically significant? No, of course not, because the study was not set up to detect that difference. But is it clinically meaningful? Quite possibly, especially if you are a patient whose chance of improvement increased as a result of adhesiolysis. Had Swank et al. asked the question in the first place whether they could detect this sort of difference, they would have planned to recruit more patients.

Failure to account for adhesion reformation in effect size determination

Let us assume for a moment that all adhesions cause pain. By performing adhesiolysis, and adhesions are cut, the source of pain is removed. So in the best case, none of the patients undergoing adhesiolysis would ever have pain again.

But there is a problem. Adhesions can and do reform. Adhesions reform about 75% of the time (Wiseman et al., 2003) when no barriers are used. As the Swank study does not specify if adhesion barriers were used, we contacted Dr. Swank who confirmed that they were not. Now that we have assumed that all adhesions cause pain, and that adhesions reform at a rate of 75%, and that no barriers are used, it follows that only 25% of the patients at best would be expected to improve. This is somewhat below the 35% effect size used in the Swank study. But the problem is compounded by the finding that 42% of the patients improved without adhesiolysis, leaving only 58% of the patients who could potentially improve due to adhesiolysis alone. With 25% of these patients improving due to adhesiolysis we calculate an overall improvement rate of 14.5% (0.25 x 58% = 14.5%), essentially the exact % improvement (15%) observed in this study.

Using this calculation, it is obvious that the effect size was likely inappropriate, leading to an underpowered study incapable of demonstrating an incremental improvement in 15% more of the patients treated by adhesiolysis, even if the improvement truly existed.

As Roman et al, (2009) point out, one wonders what results would have been obtained had adhesion barriers been used.

5.4 Is not being different the same as being the same?

In addition to concluding that adhesiolysis is no different from laparoscopy only, the discussion in Swank et al., implies that they are the same. Indeed the Powerpoint presentation associated with the AHRQ report asserts:

- "Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life." (Slide 17)

Showing that two groups are not different is not the same as saying that they are the same. But to say that the two treatments are the same, we would need to set up the study differently. Instead of asking:

- what *minimum* difference between the treatments will convince us that there is a difference? (i.e. are they different?)

we ask:

- what is the *maximum* difference up to which we would be comfortable in saying that the two treatments are the same? (i.e. are they the same?)

For the "are they different?) question we may well choose a *minimum* difference of say 35% (as was done in the Swank study), but for the "are they the same?" question we may only be comfortable in choosing a *maximum* difference of say 10% beyond which we are not comfortable in saying they are the same. So you will see that there is a sort of statistical "no man's land" between these two ideas and:

- Failing to show that two things are different is not the same as saying they are the same

This has consequences for our sample size calculation. It takes many more patients to be able to detect a difference, if it really exists, of 10% than one of 35%. So to be able to conclude that the two treatments are the same (i.e. statistically equivalent) would require many more patients. And that mistake was exactly what took place here. Indeed, Roman et al., (2009) provide a calculation to show that the two treatments are not the same, i.e. not equivalent (within 10% of each other) but are careful not to suggest that they are different and venture into another version of statistical "no man's land" where:

- Failing to show that two things are the same is not the same as saying they are different

5.5 No relationship between sample size calculation and actual analyses performed

Although the sample size calculation performed in the Swank study was based on the use of Fisher's Exact Test, the analyses presented used Mann-Whitney, Wicoxon or Chi-square tests. What kind of data exactly were to have been subjected to Fisher's Exact Test is unclear, and the paper fails to report any data that have any bearing on the power analysis, again raising the question of appropriateness of the sample size calculation.

The data that most appropriately could have been subjected to Fisher's Exact Test are those found in Figure 2 of the paper when stratified simply in terms of success/failure or any improvement vs. no change or no improvement, i.e.:

57% of 52 patients = 30 improved with adhesiolysis
42% of 48 patients = 20 improved with laparoscopy alone

Applying Fisher's Exact Test
p = 0.08 (1 tail), 0.16 (2 tail)
2 tail Odds Ratio (95% CI) = 1.909 (0.862, 4.227)

Although not achieving statistical significance, a p value of 0.08 (being close to the conventional threshold of 0.05) is sufficient reason to suspect that the two treatments differ rather than to declare that the two treatments are similar. Of course this suspicion must be confirmed with more definitive study.

5.6 Possible bias by inappropriate pre-randomization treatment of selected patients

The Swank study mentions that three of the eligible patients were treated by enterolysis (adhesiolysis involving the bowel) prior to randomization. We confirmed with Dr. Swank that this was indeed the case and that this is a source of bias. Dr. Swank also confirmed that pain did improve in these patients. Adding the 3 successes from the pre-randomized treatment to the improved group and rerunning Fisher's Exact Test

(30+3)/(52+3) = 60% of 55 patients improved with adhesiolysis
42% of 48 patients = 20 improved with laparoscopy alone

Applying Fisher's Exact Test
p = 0.048 (1 tail), 0.077 (2 tail)
2 tail Odds Ratio (95% CI) = 2.1 (0.95, 4.616)
1 tail Odds Ratio (95% CI) = 2.1 (1.084 -4.067)

This re-analysis, albeit *post hoc* and using at least a 1 tail test shows that there is basis, albeit with a number of caveats, that there is a benefit of performing adhesiolysis.

5.7 Methodological flaws and the classification by AHRQ of the study as "Good"

Given the discussion in 5.6, the Swank study is clearly not "free from bias" as described in Table E1 of the AHRQ report.

In addition to this methodological flaw, more than 20% of participants in the Swank study did not likely meet the AHRQ inclusion criteria.
The AHRQ report does not allow for the inclusion of studies where more than 20% of the participants did not meet the AHRQ inclusion criteria. The Swank study was a study of abdominal pain and not chronic pelvic pain. 13% of the patients were male. Even in the remaining 87% of patients who were female some of the pain may not have met the report's definition of female CPP. If only 8% (not an unreasonable number) of these would have had only dyschezia, dysuria or dyspareunia (excluded from the definition of chronic pelvic pain – see ES1 and p1) or other clearly non-pelvic pain, then the Swank study would have more than 20% of its participants who do not meet the AHRQ criteria, thus preventing the study from being included in the AHRQ analysis.

At best, these methodological flaws may justify downgrading the study from its current rating of "Good".

5.8 Subpopulations in the Swank Study

Although not part of the published study, Dr. Swank mentioned to us that he felt there was a subgroup of younger patients with limited adhesions who may have benefited from adhesiolysis. This may be worthy of further exploration.

6 Are we missing the point?

Despite the Swank study lacking a third arm in which patients who are candidates for laparoscopy/ adhesiolysis are followed for 12 months (even assuming this could be blinded), Swank et al., concluded that both adhesiolysis and laparoscopy relieved pain. Ignoring for a moment the problem of how such a conclusion can even be reached without the third arm and even accepting that adhesiolysis does not contribute to an improvement in pain, 57% of patients undergoing laparoscopy and adhesiolysis did show some improvement in pain after 12 months.

If the implied conclusion that adhesiolysis is of no additional benefit is adopted by the surgical community, will it mean that patients will still be offered a diagnostic laparoscopy when other pathology has already been ruled out and the opportunity to be one of 42% of patients who benefit from that alone? Of course not. Patients will likely be offered nothing.

7 Conclusion

The foregoing analysis is not intended to convince anyone that adhesiolysis is highly beneficial for treatment of pelvic pain. Given the issues noted regarding the Swank study itself, or its interpretation by the AHRQ report, any conclusion or implication that adhesiolysis does not benefit pelvic pain must be challenged. Clearly more research is needed to clarify this important issue. Above all, the research should at least build on the innovative study designed by Swank and his colleagues and attempt to overcome the shortcomings we have highlighted.

In the meantime, let this not be a cause to remove adhesiolysis, or even laparoscopy as an option for the treatment of pelvic or abdominal pain, provided other, less invasive measures have been fully explored.

8 APPENDIX: Correspondence with Dr. Jeff Andrews, Lead Author

Note that typos have not been corrected, to preserve integrity of original correspondence

8.1 Original email to Jeff Andrews 5/22/12

Subject: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study
Date: 5/22/2012 5:55:22 P.M. Central Daylight Time
From: Synechion@aol.com
To: jeff.andrews@vanderbilt.edu, [other recipients' addresses redacted]
CC: david.wiseman@adhesions.org

Dear Dr. Andrews
Your nurse Rebecca was kind enough to leave me a message with your email address after I had contacted your office yesterday.

I am writing concerning your AHRQ report (and associated CME) :

Noncyclic Chronic Pelvic Pain Therapies for Women: Comparative Effectiveness
http://www.effectivehealthcare.ahrq.gov/ehc/products/195/808/CER41-Pelvic-Pain_20120112.pdf

I did take the CME quiz and completed an evaluation with most of my comments below, but I wanted to make contact with you directly.

Summary

In general the report and the CME were excellent and much needed. My one concern is regarding the discussion on adhesiolysis, the 2003 Swank study that it references in several places and the conclusion and impression that the report and its CME slides might leave with the reader that "adhesiolysis does not help pain, it is not worth performing".

As I hope to show there are a several flaws in the interpretation of the study and while their consideration does not convince one that "adhesiolysis certainly reduces pain", they should at least leave the reader with a more balanced impression that:

"The relationship between adhesions and pain is very complex. The few studies that address whether or not adhesiolysis benefits patients with CPP are limited either by size, design or interpretation, but nonetheless suggest that adhesiolysis may benefit some patients."

Left as is, I am fearful that this report, as far as its discussion on adhesiolysis, will be relied by payers and other policy makers to deprive many thousands of patients of an avenue of relief, one that may be the only one left after many years of futile search.

My objective is to request that by way of amendment of revision in future versions of this report, its executive, consumer and clinician summaries and the CME program that accompanies it, this balance is restored. Further the question of adhesion barriers, and the effect of a diagnostic laparoscopy alone should be addressed.

Introduction

By brief way of introduction I have been conducting and publishing on pre-clinical and clinical adhesions research for nearly 25 years. The first 9 years of these I spent at Johnson & Johnson where I ended up heading the Interceed R&D program. In 1996 I left to found Synechion, a company providing R&D consulting services focussing on adhesions. For full disclosure, my clients have with financial/commercial interests in adhesions, as do I. I also founded the International Adhesions Society which through its web site and other activities provides support, impartial information and advocacy for patients with adhesions, without advocating any particular products. We have conducted research of our own, some of which you can read about here: http://adhesions.org/Wiseman2008SeminreprodMed26p356CAPPS.pdf

Although I am an advocate for the use of adhesion barriers and adhesiolysis (and much of my business depends on it), I certainly understand that there is a complex relationship between adhesions, pain and related disorders. Indeed in order to shift the paradigm from a surgical one that says "adhesions = pain = surgery = cure", I started using the terms Adhesions Related Disorder (ARD) and CAPPS (Complex Abdomino-Pelvic & Pain Syndrome) to shift the paradigm to one in which the complex nature of chronic pain and related conditions is considered in an integrative manner before resorting to surgery. Indeed I was instrumental in the conception and establishment of the world's first multidisciplinary center for adhesions and CAPPS at Celebration Health in FL: http://www.adhesionscenter.com/

What the report says about adhesiolysis

The overall impression of the report's conclusion regarding adhesiolysis I believe is to be found at the first place in the executive summary where it is mentioned, ie p ES6 (see also ES7)

"One good-quality RCT evaluated laparoscopic lysis of intraabdominal adhesions (Swank) and reported no improvement in pain scores over diagnostic laparoscopy."

"With two RCTs, one of fair and one of poor quality, we assessed the strength of evidence as low for the lack of efficacy of LUNA to improve pain status over diagnostic laparoscopy alone and low for the effects of adhesiolysis on pain and quality of life (one good-quality RCT)."

In other places similar statements are to be found:
p51 - The evidence is insufficient to conclude that surgical intervention is either effective or ineffective for the treatment of CPP.
p53 - The strength of evidence for the effect of adhesiolysis on pain status was low based on one good quality RCT.93
p70 - Aside from the lack of benefit reported for adhesiolysis, (Swank) little evidence demonstrates the effectiveness of surgical approaches

The report in a number of places gives language that could modify the strength of this conclusion, notably on ES6 and p53 which state that the conclusion is based on [onl] one good-quality RCT. The only other modifying language is on p37:

"The potential effects of diagnostic laparoscopy in women with CPP have not been fully studied. Improvements following post-diagnostic laparoscopy have been reported but whether these improvements are “real” or “placebo” remains to be determined. Among studies using diagnostic laparoscopy as the comparator to an active intervention, diagnostic laparoscopy was used primarily as a diagnostic tool to try to identify potential pathologic explanations for CPP, and patients were randomized after the diagnostic laparoscopy. In these studies, patients were randomized at the time of surgery, after the diagnostic portion of laparoscopy, to receive additional treatment intervention or not."

For the CME slides that accompany the report:
www.effectivehealthcare.ahrq.gov/tasks/sites/ehc/assets/file/chronic-pelvic-pain.ppt
the conclusion is even more condensed:
slide 17: "Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life."
slide 20: "Among surgical approaches for CPP, both LUNA and laparoscopic adhesiolysis were not found to be superior to diagnostic laparoscopy."

The body of the report certainly conveys the complexity of CPP and begins to convey the still largely mysterious relationship between adhesions and CPP. The single reference to the Swank study without elaboration of its strengths and weaknesses fails to convey that complexity. I realise that for the purposes of CME (which is what most people will read) there is a need to summarise and simplify, but I believe it was done at a cost that will reflect itself in the way physicians interact with their CPP patients.

The Swank Study
The Swank study was relatively small (n=100) and showed that 42% of control patients benefited somewhat from laparoscopy only and 57% benefited with additional adhesiolysis (some 35% relative improvement). Page C47 of the report only lists Swank's "Pain Free", and "Much Improved" categories but not his "Improved" category which is where a difference between the groups appears (15% vs 30%).

Swank certainly failed to show a statistical significant difference between the groups but his conclusion (carried over into your report) that "it is not more beneficial than diagnostic laparoscopy alone" must surely be subject to a Type II error and inadequate powering of the study. We do not know what % of patients had a recurrence of adhesions that could explain pain. Indeed, the difference in the percent of patients with pain reduction in the adhesiolysis group (vs the control group) is consistent with the expected degree of improvement from the rates of adhesion reformation after adhesiolysis. Thirdly, we do not know in what % of patients were adhesion barriers used, if any.

In addition to the problem of adhesion reformation, the lack of (statistically significant) benefit may have been due to a) adhesions were not the cause of pain in some patients; b) the failure to remove scarring at the tissue surface (as opposed to lysing the "between-tissue adhesions" which may have been distorting nerves - causing pain; c) the failure to address neural changes resulting from the chronic nature of the pain; d) all of the above.

One possible outcome from the study is that laparoscopy itself (possible the act of performing general anesthesia an/or insufflation) is sufficient to effect at least a temporary reduction in pain. Certainly, anecdotally, this has been our experience in speaking to hundreds of "adhesions" patients over a period of some 16 years. I am not well versed in the LUNA literature, but it seems that there too laparoscopy alone has an effect on pain. This point is briefly addressed on page 37 of the report.

Conclusion

As the report and course correctly convey, further work is needed to identify the most effective surgical and non-surgical methods of treating CPP and to understand more fully the mechanisms of CPP. In the case of adhesions something is happening other than just a direct effect of two tissues being abnormally connected by scar tissue and so declarative statements of the kind made here about adhesiolysis (albeit with a disclaimer about the "low" level of evidence etc.) might label the issue unfairly as one that has been resolved.

At the time of its publication Dr. Michael Diamond of Wayne State University, and advisor to the IAS and someone with whom I have collaborated on many adhesions projects for nearly 25 years wrote a letter to the editor of the Lancet stating many of these points. Unfortunately the letter was not published, but I am pleased to note a more recent critique by Roman et al., (2009) on similar statistical and other grounds who state *"The trial should therefore not have concluded that the 2 surgical procedures were equivalent. By doing so, it is likely that numerous surgeons have abandoned laparoscopic adhesiolysis on the basis of this statement."* Indeed on the basis of these remarks might I suggest that the Swank study in the report be rated (page E-1) as something less than "Good".

Please allow me the liberty of copying Dr. Michael Diamond (at Vanderbilt as a medical student, resident and Director of Rep-Endocrin) with whom I have briefly discussed this matter, although he has not reviewed this email. I am also copying Dr. Horace Roman with whom I have never corresponded, but on the basis of his paper suspect that he, like Dr. Diamond, may be able to contribute meaningfully to this discussion.

I would very much appreciate the opportunity to discuss with you this issue and to collaborate in updating this particular section of an otherwise outstanding and much needed work in its various forms. I await the pleasure of your reply.

Sincerely

David Wiseman Ph.D., M.R.Pharm.S.
Founder, International Adhesions Society (IAS)
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Dallas, TX 75248
972 931 5596
972 931 5476 FAX
469 939 5596 cell

Roman, H.; Hulsey, T. F.; Marpeau, L., and Hulsey, T. C. Why laparoscopic adhesiolysis should not be the victim of a single randomized clinical trial. Am J Obstet Gynecol. 2009 Feb; 200(2):136.e1-4
Randomized controlled trials may provide erroneous conclusions when the null hypothesis is not rejected because of insufficient analysis statistical power. The authors dispute the conclusion of a randomized controlled trial that compared chronic pain relief rates following laparoscopic adhesiolysis and diagnostic laparoscopy and recommended abandoning laparoscopic adhesiolysis. In the trial, the observed difference between pain rates (15%) was inferior to that expected (35%). On the basis of this result, we calculated the 90% confidence interval of the true difference, whose limits of -1% and 31% were found to fall outside the predetermined equivalency interval (-10% to 10%). The trial should therefore not have concluded that the 2 surgical procedures were equivalent. By doing so, it is likely that numerous surgeons have abandoned laparoscopic adhesiolysis on the basis of this statement. In any randomized trial, a calculation of statistical power is required each time that the null hypothesis cannot be rejected.

Swank DJ, Swank-Bordewijk SC, Hop WC, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet. 2003 Apr 12;361(9365):1247-51.

8.2 Additional email to Jeff Andrews 5/30/12

From: Synechion@aol.com [Synechion@aol.com]
Sent: Wednesday, May 30, 2012 1:36 PM
To: Andrews, Jeff [other recipients' addresses redacted]
Subject: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study

Dear Dr. Andrews
I am following up on my email of just over a week ago. I have this morning spoken with Dr. Swank who was kind enough to clarify some items mentioned in his paper.

1. Adhesiolysis was performed in patients excluded from the study.
As the paper states, there were three patients in whom lysis of bowel adhesions was performed prior to the randomization. Dr. Swank told me that the pain in these patients did certainly improve. Accordingly he could certainly appreciate why it may have been more appropriate to include them in the study. So I re-ran the numbers.

Whether you add these patients to the 52 randomized patients and regard them as successes, or add them to the 48 patients randomized to laparoscopy only and regard them as failures, the calculation seems to come out the same:

As original: 57% of 52 patients improving with adhesiolysis = 30 AND 42% of 48 patients improving with laparoscopy = 20

A Fisher's Exact test gives: p = 0.08 (1 tail), 0.16 (2 tail), 2 tail Odds Ratio (95% CI) = 1.909 (0.862, 4.227)

Adding the 3 successes from the pre-randomized treatment gives
60% of 55 patients improving with adhesiolysis = 33 AND 42% of 48 patients improving with laparoscopy = 20

and
A Fisher's Exact test using these new numbers gives: p = 0.048 (1 tail), 0.077 (2 tail), 2 tail Odds Ratio (95% CI) = 2.1 (0.95, 4.616)

Since we are post hoc, and have reason to believe there is a benefit, we could well justify a 1 tail test. Adjusting the CI for the Odds ratio for one tail would give an interval of 1.084-4.067

So now the results seem to come out more in favor of adhesiolysis vs. laparoscopy alone, than before.

2. Sub-populations
Dr. Swank mentioned that he felt there was a subgroup of younger patients with limited adhesions who may have benefited.

3. Influence of adhesion barriers
Dr. Swank confirmed that there are were no barriers used in the study.

With the same caveats as in my earlier email, there is even more reason to appreciate that even if the results of this study do not achieve statistical significance, they certainly approach significance closely enough to temper the top-line messages contained in the AHRQ report and associated materials that "Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life."

I await the pleasure of your reply on this and my previous email.

Sincerely

Sincerely
David Wiseman Ph.D., M.R.Pharm.S.
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8.3 Brief Response from Jeff Andrews 6/5/12

Subject: RE: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study
Date: 6/5/2012 3:46:13 P.M. Central Daylight Time
From: jeff.andrews@Vanderbilt.Edu
To: Synechion@aol.com

Dr Wiseman
The way things work at AHRQ/EHC, AHRQ must respond to comments and questions.
I must provide my thoughts to them and they have the responsibility to answer.
I have forwarded your Emails to them, and I am sure you will be receiving a response.
Thanks very much

Jeff Andrews, MD

_____

8.4 Full Initial Response from Jeff Andrews 6/14/12

Subject: RE: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study
Date: 6/14/2012 1:33:56 P.M. Central Daylight Time
From: jeff.andrews@Vanderbilt.Edu
To: Synechion@aol.com
CC: david.wiseman@adhesions.org

Dear Dr Wiseman
please forgive the inordinate delay in this response
I have attached a letter to you
thanks again for your interest and careful commentary

Jeff
Jeff Andrews, MD, FRCSC
Associate Professor of Obstetrics and Gynecology
Senior Scientist in the Vanderbilt Evidence-based Practice Center
Associate Editor for the Effective Health Care Program, AHRQ

Attached response from Jeff Andrews:

Dr. Wiseman,
Thank you for your interest in the report on Management of Noncyclic Chronic Pelvic Pain. As described in the report, this comparative effectiveness review was specifically focused on treatments for noncyclic chronic pelvic pain. The report's key questions and the inclusion/exclusion criteria for studies in the report were developed with a team of technical experts and went through public review and comment (June 3, 2010-July 1, 2010). As such, the criteria by which studies were selected were as follows:

- Original research
- Population composed of adult women (≥18 years of age) with noncyclic or mixed cyclic/noncyclic CPP undergoing surgical or nonsurgical treatment for CPP (studies with a primary focus on coexisting conditions (vulvodynia, irritable bowel syndrome, etc.) or on cancer pain or pregnancy-related pain were not included)
- Study had to be either a controlled trial or prospective cohort study with at least 50 women with noncyclic/mixed CPP or cross-sectional study or case series with at least 100 women with noncyclic/mixed CPP and reporting relevant harms or prevalence data; for those studies including

women and men or adult women and adolescents, we retained the study if least 80% of the population was adult women with noncyclic/mixed CPP

- Studies had to address an outcome of interest (pain status, functional status, quality of life, patient satisfaction, harms/adverse events of nonsurgical therapies)
- Studies had to include extractable on outcomes of interest

We would not have included studies on adhesiolysis if the patient populations or study designs did not meet criteria for inclusion. Therefore, as noted, this is not intended to be an analysis of adhesiolysis writ large, but included those adhesiolysis studies that focused specifically on our target patient population. This set included the one RCT that you comment about, that of Swank et al. As noted in the report, we assessed this study to be of good quality. You note that you "reran" the numbers adding patients not included in the published study (post hoc analysis). Accepted methodology for systematic reviews does not include adding patients not in the study to the statistical analysis.

We also alert you that the conclusions on strength of evidence in the report should not be conflated with measures of effectiveness. Strength of evidence considers both the observed effectiveness of interventions and the confidence that we have in the stability of those effects in the face of future research. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence, and it can be regarded as insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, both in terms of quantity and quality, as well as the degree to which the entire body of current research provides a consistent and precise estimate of effect. Interventions that have demonstrated benefit in a small number of studies but have not yet been replicated using the most rigorous study designs will therefore have insufficient or low strength of evidence to describe the body of research. Future research may find that the intervention is either effective or ineffective. The overall strength of evidence could be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect). In this case, the strength of evidence was evaluated as low, indicating low confidence that the evidence reflects the true effect, and furthermore, that future research is likely to change the estimate of effect. We think you are in agreement with us; you are not confident that adhesiolysis does not benefit noncyclic chronic pelvic pain, and we would all welcome further research to clarify the uncertainty.

As you note in your comments, the role of adhesions in chronic pelvic pain has not been established. More research is needed both on this relationship and on interventions directed at adhesion prevention and adhesion management, as we have noted in our report.

Sincerely,
Jeff Andrews, MD

8.5 Reply to Jeff Andrews 6/29/12

Subject: Re: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study
Date: 6/29/2012 6:10:20 P.M. Central Daylight Time
From: Synechion@aol.com
To: jeff.andrews@Vanderbilt.Edu
CC: [other recipients' addresses redacted]

Dear Dr. Andrews

Thank you for your detailed reply. I am sorry that I was unaware of the report during its comment period and would certainly have been willing to provide comments.

Summary

Based on your statement:

"In this case, the strength of evidence was evaluated as low, indicating low confidence that the evidence reflects the true effect, and furthermore, that future research is likely to change the estimate of effect. *We think you are in agreement with us; you are not confident that adhesiolysis does not benefit noncyclic chronic pelvic pain*, and we would all welcome further research to clarify the uncertainty."

In affirming our agreement let me point out that your last sentence is the bottom line message that I believe is most appropriate to convey in the report and the accompanying CME presentation. Again I am concerned that the wording of various summary statements does not adequately convey this message. For style reasons only let me suggest that the report's statement on p51 is the one that should be used in the discussion of adhesiolysis: *"The evidence is insufficient to conclude that surgical intervention is either effective or ineffective for the treatment of CPP."*

I am therefore writing to request that this statement is the one used in the report summary and the accompanying CME to fairly reflect the state of the art regarding adhesiolysis and CPP. I realise that it may not be possible to amend the report itself, but possibly to amend the web-based summaries for example:

- the patient version: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1032

- the physician version: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=931

To stress – I am not suggesting revising any of the findings of the report, merely providing a balance in the summary sections that already exists within its body.

As I mentioned in my original email, I have taken the liberty of including in this discussion, Dr. Michael Diamond with whom I have worked for many years on many adhesions projects. For full disclosure we both have financial interests in the business of adhesions and consult with a number of companies working in that area. We will be happy to provide further details on request. In this matter, neither of us have been retained or induced by any client to make these overtures to you.

Because it may not be possible to amend the report itself and because it did not appear in the peer reviewed literature, we are considering submitting an editorial to one of the main GYN journals discussing the report, the issue of adhesiolysis and pain, as well as calling for definitive research on the matter. We invite your participation in this endeavor as a co-author. We are also considering submitting a grant application to conduct a high quality study to resolve the issue of adhesiolysis and pain. Again we invite your participation and collaboration in this endeavor.

Some further analysis and discussion is found below. We await the pleasure of your reply.

Sincerely

David Wiseman

Cc Dr. Michael Diamond

Further Analysis

Concerns
If your statement:
"We think you are in agreement with us; you are not confident that adhesiolysis does not benefit noncyclic chronic pelvic pain"

reflects most fairly your analysis, then, reiterating my concerns – that even though the body of the report does limit the import of the Swank study in several places, the summary sections and the accompanying CME presentation (which is what most readers will peruse) convey the converse message namely:

"We are not confident that adhesiolysis does benefit noncyclic chronic pelvic pain"

Some might even understand this as meaning: "*Adhesiolysis definitely does not benefit noncyclic CPP."*

With this sort of language, and in the absence of good quality studies that provide a high SOE, I am concerned that the report's summary statements will find their way into policies within FDA, DHSS or insurance providers prematurely. This will have all sorts of repercussions that will deny treatment to patients that until proven otherwise, could benefit them, given proper informed consent.

The summary found on the web page:
http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1029

comes close to providing some perspective:

- No significant difference was found between laparoscopic adhesiolysis and diagnostic laparoscopy for improving pain status and quality of life. [Low SOE]

Evidence from one RCT in patients with adhesions showed that both laparoscopic adhesiolysis and diagnostic laparoscopy significantly improved pain scores and quality of life at 12 months of followup, with no significant differences between the two interventions.

The statement that follows may serve to provide more balance:

- Evidence was insufficient to permit meaningful conclusions about the relative effectiveness of the following interventions in improving pain status. [Insufficient SOE]
  - Surgical versus non-surgical therapy
  - LUNA versus uterosacral ligament resection

although it is not clear that this includes the adhesiolysis work.

Statement Analysis
The main statements in question are as follows:

pES6 (see also ES7): "One good-quality RCT evaluated laparoscopic lysis of intraabdominal adhesions (Swank) and reported no improvement in pain scores over diagnostic laparoscopy."

"With two RCTs, one of fair and one of poor quality, we assessed the strength of evidence as low for the lack of efficacy of LUNA to improve pain status over diagnostic laparoscopy alone and low for the effects of adhesiolysis on pain and quality of life (one good-quality RCT)."

Even accepting that the Swank study is "good" (see below) I hope you will agree that the above statements convey the impression that

"We are not confident that adhesiolysis does benefit noncyclic chronic pelvic pain"

more than

[we] *"are not confident that adhesiolysis does not benefit noncyclic chronic pelvic pain"*

If the issue is the ability to convey the message succinctly for the report, then p51 was able to rise to the challenge:

"The evidence is insufficient to conclude that surgical intervention is either effective or ineffective for the treatment of CPP."

Let me suggest that this statement is the one appropriate to represent fairly the state of the art regarding adhesiolysis and CPP.

The situation regarding the CME slides accompanying the report is similarly problematic www.effectivehealthcare.ahrq.gov/tasks/sites/ehc/assets/file/chronic-pelvic-pain.ppt

The key statements are found in:

Slide 17:
"Laparoscopic adhesiolysis and diagnostic laparoscopy were similarly effective in improving pain scores and quality of life."

> Evidence was based on 1 RCT in patients with CPP associated with adhesions who were followed up for 12 months. *Strength of evidence*: low

And slide 20:
"Among surgical approaches for CPP, both LUNA and laparoscopic adhesiolysis were not found to be superior to diagnostic laparoscopy."

Should the Swank study should be regarded a "good quality"?
With the Swank study classified as "good" the above arguments are still valid. How much more so if one considers the analysis below suggesting that the Swank study should be downgraded from "good".

Possible bias by excluding enterolysis patients
I pointed out in my original email to you, as well as those described in Roman's paper, a number of methodological flaws in the Swank study. Since then, Dr. Korell of Germany pointed out to me another issue that I had not focused on earlier relating to three patients in whom enterolysis was performed. Wishing to clarify the status of these patients I telephoned Dr. Swank who kindly clarified that this was done prior to randomization. He agreed that this was therefore the source of some potential bias. Given freedom from bias as one of the criteria for grading a study, and the rating of this study as being "free from bias" (Table 17), let me suggest that the study be downgraded from "good" on this basis alone, in addition to the other flaws mentioned.

I understand that your report did not allow for post hoc analysis, but my re-running of the numbers merely satisfied my curiosity as to what effect including those patients would have. Even if it were sufficient to upgrade the quality of evidence for adhesiolysis, the study quality should still be downgraded.

You are certainly free to verify my conversation with Dr. Swank. His contact details are:
Dr D J Swank
[contact details redacted]

Power analysis: assumptions not met
Some further points I had not mentioned previously relate to the power analysis about which the Swank paper states.

"We calculated that a sample size of 120 patients was needed, on the assumption that 90% of our patients had adhesions, that there is a 25% reduction in pain attributable to placebo, and that 60% of patients would have pain relief 1 year after laparoscopic adhesiolysis. Furthermore, 50 patients were needed in each group to detect a 35% reduction in pain after laparoscopic adhesiolysis compared with laparoscopy, with a power of 80% for a significance level of 5% (two-sided) with Fisher´s exact test."

Several points:

1. Unlike the AHRQ report (p36) which cites published recommendations to sets an effect size at 30%, the Swank paper provided no basis for selecting 35% as the effect size. Of course there is great debate as to what constitutes a "clinically meaningful effect". Any discussion I have witnessed or been a part of, for example in regard to FDA approval of anti-adhesion products, has set a minimum as 20%. The AHRQ report sets this as 30% (p36). So 35% would seem a tad high meaning that had 30% been selected, the power analysis would have calculated a larger sample size, possibly altering the level of final statistical significance.

In its discussion of sample size (p36), the AHRQ report lowered its requirement for sample size from 350 to 50, allowing for some compromise for the reasons fairly stated. This said it was not necessary to compromise across the board and let me suggest that studies that deviated from the basic criteria (other than sample size) should have received a lower rating as to quality.

2. Even with the 35% effect size, the power analysis assumed a placebo effect of 25%, which turned out much higher. Thus one major assumption of the power analysis was not met.

3. The power analysis was predicated on a Fisher's exact test and yet all the analyses presented used Mann-Whitney, Wicoxon or chi-square tests. What kind of data exactly were to have been subjected to Fisher's exact test is unclear, and the paper fails to report any data that have any bearing on the power analysis.

Perhaps most appropriately Fisher's exact test would be used to compare success/failure ie any improvement vs. no change or no improvement. Using data in Figure 2:

> A Fisher's Exact test gives: p = 0.08 (1 tail), 0.16 (2 tail), 2 tail Odds Ratio (95% CI) = 1.909 (0.862, 4.227)
>
> Adding the 3 successes from the pre-randomized treatment gives 60% of 55 patients improving with adhesiolysis= 33AND 42% of 48 patients improving with laparoscopy= 20
>
> And a Fisher's Exact test using these new numbers gives: p = 0.048 (1 tail), 0.077 (2 tail), 2 tail Odds Ratio (95% CI) = 2.1 (0.95, 4.616)

Again these post hoc analyses are not intended to convince anyone that adhesiolysis is highly beneficial, not merely to illustrate that were a number of methodological flaws in the study which should contribute to a lower than "good" rating.

Lastly, let me emphasise that despite the above comments, I believe that Swank and his colleagues performed a novel and important study which has certainly contributed to the literature (and clearly discussion !!) about CPP and adhesions. As we both agree, more research is needed to clarify this issue.

8.6 Follow up email sent to Jeff Andrews July 17 2012

From: Synechion@aol.com
Sent: Tuesday, July 17, 2012 6:18 PM
To: Andrews, Jeff
Cc: [other recipients' addresses redacted]
Subject: Re: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study

Just following up on this sent on 6/29/12
Thanks
DW

8.7 Response from Jeff Andrews about July 20 2012

thank you for your interest and extensive efforts
at this juncture, we cannot change the report
at the first revision, we can incorporate your suggestions
evaluation for revision and update occurs every 6 months, and it is 6 months since the online posting

with regard to your future publication, I respectfully decline the offer to be included as a co-author

in a way, we both see a glass that contains 1/2 it's volume in water - you see the glass as half-full and encourage more research to demonstrate the benefits of adhesiolysis for CPP, and we see the glass as half-empty and encourage more research to determine if there is any benefit of adhesiolysis for CPP

best regards,
Jeff

Jeff Andrews, MD, FRCSC
Associate Professor of Obstetrics and Gynecology
Senior Scientist in the Vanderbilt Evidence-based Practice Center

8.8 Response to Jeff Andrews about July 22 2012

Subject: Re: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study
Date: 7/22/2012 3:53:20 P.M. Central Daylight Time
From: Synechion@aol.com
To: jeff.andrews@Vanderbilt.Edu
CC: [other recipients' addresses redacted]

Dear Jeff

Thank you for this response. It looks like there will some revisions soon. If it is appropriate, we would be happy to provide comments before publication.

Half-full or half empty? - not sure about that, but we certainly agree that more work is needed. I'm certainly up for a FULL glass of beer that we can discuss this over !!
Hopefully your report will help to highlight the need for it. A couple of additional points:

1. The Swank study was a study of abdominal pain and not CPP. In fact 13% of the patients were male. The report does allow for the inclusion of studies where no more than 20% of the participants were outside of the inclusion criteria.
But even in the 87% female patients some of the pain may not have met the report's definition of female CPP. If only 8% (not an unreasonable number) of these would have had dyschezia, dysuria or dyspareunia (it seems from the intro that the defintion of CPP excludes these) or other clearly non-pelvic pain, then the study would go below the 80% threshold.

(The study is still worthy of discussion, but with these additional issues). The study does not stratify the data by gender or by whether the pain is CPP or non-CPP.

A related point that would be worth discussing, at least to guide future studies, is the
issue of endometriosis, possible differences between groups in treatment and recurrence could confound results further. The Swank study did not address this issue, but future studies should.

2. A number of the members of the International Adhesions Society have expressed obvious interest in this issue. I would like to make a posting on our web site/FB page referencing the report, the discussion of adhesiolysis and what I regard as the friendly, healthy and positive discussion between us that is about to result in a revision that will incorporate some of our comments. Before doing so I would like to ask whether you would consider this as being antagonistic to your efforts in anyway. I certainly do not intend it that way, or want it to be perceived that way.

With regards

David Wiseman
Synechion, Inc.
International Adhesions Society

8.9 Follow up to Jeff Andrews October 10 2012

From: Synechion@aol.com
Sent: Wednesday, October 10, 2012 2:21 PM
To: Synechion@aol.com; Andrews, Jeff
Cc: [other recipients' addresses redacted]
Subject: Re: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study

Dear Jeff
Any news on when the revisions to the report etc. will be made?
Will you be at the IPPS meeting next week? - I will be there.
Regards
David Wiseman

8.10 Follow up from Jeff Andrews October 16 2012

Subject: RE: New info on: AHRQ report on Pelvic Pain: Adhesiolysis-Swank study
Date: 10/16/2012 8:53:03 A.M. Central Daylight Time
From: jeff.andrews@Vanderbilt.Edu
To: Synechion@aol.com

CC: [other recipients' addresses redacted]

hi David!
we have not been notified about revisions as of now
as you may know, the budget to AHRQ has been reduced, the ARRA funding has completed, and Sequestration is looming
we are waiting to see what projects will be funded - I doubt we will hear anything now before Jan

I wish I could go to IPPS
during the Great Recession, we have had to cut our travel budgets, so I can't go to as many meetings as I would like
if you are going to Tweet from the meeting, let me know your handle and I will sign up for your feed

thanks
Jeff

Jeff Andrews, MD, FRCSC
Specialist, Associate Professor of Obstetrics and Gynecology
Senior Scientist in the Vanderbilt Evidence-based Practice Center, Institute for Medicine and Public Health

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10 Acknolwedgement

I wish to thank Dr. Michael Diamond for his wise counsel and agreement in this matter. I also wish to thank Dr. Dingeman Swank for his willingness to discuss his study. The comments regarding his study are not intended to denigrate it. We believe that Dr. Swank and his colleagues have made an important contribution to the medical literature which, it is hoped will help to bring clarity to a long neglected subject. Lastly I wish to thank Dr. Jeff Andrews, the lead author of the AHRQ report for his willingness to engage in an honest and productive discussion and to offer to revise the AHRQ report.

11 Disclosure and Author Background

The author has been conducting and publishing on pre-clinical and clinical adhesions research over 25 years. The first 9 years of these were spent at Johnson & Johnson where he ultimately headed the Interceed R&D program. In 1996 he left to found Synechion, a company providing R&D consulting services focusing on adhesions. For full disclosure, Synechion's clients may have financial/commercial interests in adhesions, as may the author or his family. The present document has not been written at the request or suggestion of any of these clients or prospective clients. The author also founded the International Adhesions Society (IAS) which through its web site and other activities provides support impartial information and advocacy for patients with adhesions, without advocating any particular products. The IAS has conducted research of its own, much of which is summarized in the paper found at http://adhesions.org/Wiseman2008SeminreprodMed26p356CAPPS.pdf

Although the author is an advocate for the use of adhesion barriers and adhesiolysis, he certainly understands that there is a complex relationship between adhesions, pain and related disorders. Indeed in order to shift the paradigm from a surgical one that says "adhesions = pain = surgery = cure", he started using the terms Adhesions Related Disorder (ARD) and CAPPS (Complex Abdomino-Pelvic & Pain Syndrome) to shift the paradigm to one in which the complex nature of chronic pain and related conditions is considered in an integrative manner before resorting to surgery. Indeed the author was instrumental in the conception and establishment of the world's first multidisciplinary center for adhesions and CAPPS at Celebration Health in FL: http://www.adhesionscenter.com/

Lastly the author recently founded KevMed, LLC. (www.kevmed.com) a company focused on the commercialization of products and services for chronic pelvic pain and related conditions. Its first product, PainShield MD, is a portable, wearable therapeutic ultrasound device shown, through research conducted through the IAS to be helpful in patients suffering from chronic pelvic pain and related conditions.

