Evidence-based clinical update: General anesthesia and the risk of delirium and postoperative cognitive dysfunction

[Mise à jour clinique fondée sur des données probantes : l'anesthésie générale et le risque de délire et de dysfonctionnement cognitif postopératoire]

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Purpose: The purpose of this structured, evidence-based, clinical update was to identify the best evidence comparing general and regional anesthesia and their influence on delirium or cognitive dysfunction (POCD) in the postoperative period.

Source: In June 2005 a structured search of MEDLINE from 1966 to present using OVID software was undertaken. Medical subject headings and textwords describing both delirium and POCD were employed. OVID's Therapy (sensitivity) algorithm was used to maximize the detection of randomized trials. The bibliographies of eligible publications were hand-searched to identify trials not identified in the electronic search. Publications enrolling children were excluded. Levels of evidence and grades of recommendations were scored using Centre for Evidence Based Medicine criteria.

Principal findings: A total of 18 unique randomized controlled trials were identified: two evaluating delirium; ten evaluating POCD; and six evaluating both. Outcomes for delirium were abstracted from eight trials that enrolled 765 patients (387 regional anesthesia; 378 general anesthesia). Outcomes for POCD were identified from 16 trials that enrolled 2,708 patients (1,313 regional anesthesia; 1,395 general anesthesia). Both delirium (11–43%) and POCD (15–25%) were relatively common in trials actively seeking these outcomes. Consistent Level 2b evidence suggests no significant increase in delirium in patients receiving general anesthesia compared with those receiving regional anesthesia. Similarly, consistent Level I evidence indicates that exposure to general anesthesia is not significantly associated with POCD.

Conclusion: Available randomized controlled trials suggest that there is no significant difference in the incidence of delirium or POCD when general anesthesia and regional anesthesia are compared.

Objectif : Identifier, par une mise à jour clinique structurée et fondée sur des données probantes, la meilleure preuve en comparant l'anesthésie générale et régionale et leur influence sur le délire ou le dysfonctionnement cognitif postopératoires (DCPO).

Source : En juin 2005, une recherche structurée a été entreprise dans MEDLINE, de 1966 à nos jours, en utilisant le logiciel OVID. Les vedettes-matières et les textes décrivant le délire et le DCPO ont été utilisés. Un algorithme thérapeutique (sensibilité) tiré de OVID a servi à optimiser la détection d'études randomisées. Les bibliographies des études admissibles ont été fouillées manuellement pour découvrir les études non repérées dans la recherche électronique. Les recherches portant sur des enfants ont été exclues. Les niveaux d'évidence et les degrés de recommandations ont été évalués selon les critères du Centre for Evidence Based Medicine.

Constatations principales : Nous avons trouvé 18 études randomisées et contrôlées originales : deux évaluaient le délire, dix le DCPO et six évaluaient les deux. Les données sur le délire ont été extraites de huit études regroupant 765 patients (387 pour l'anesthésie régionale et 378 pour l'anesthésie générale). Les données sur le DCPO ont été tirées de 16 études sur 2 708 patients (1 313 pour l'anesthésie régionale et 1 395 pour l'anesthésie générale). Le délire (11 – 43 %) et le DCPO (15 – 25 %) étaient relativement fréquents dans les études qui recherchaient activement ces résultats. L'évidence d'un niveau 2b persistant montre qu'il n'y a pas d'augmentation significative du délire chez les patients sous anesthésie générale comparée à l'anesthésie régionale. De même, l'évidence d'un niveau I persistant indique que l'exposition à l'anesthésie générale n'est pas significativement associée au DCPO.

Conclusion : Les études randomisées et contrôlées accessibles montrent que l'incidence de délire ou de DCPO n'est pas significativement différente avec l'anesthésie générale ou régionale.

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Disclosure: This work was supported by the Departments of Anesthesiology at The Ottawa Hospital and the University of Ottawa. The authors declare no commercial or non-commercial affiliations that are or may be perceived to be a conflict of interest with the work, and any other associations such as consultancies.

Accepted for publication February 10, 2006.

Revision accepted February 21, 2006.

CHANGES in cognitive function frequently complicate the postoperative course of the elderly patient undergoing non-cardiac surgery. Many patients and physicians implicate general anesthesia in the etiology of adverse cognitive outcomes; published research challenges this assumption. This clinical controversy will be addressed using the "Evidence-Based Clinical Update" structure of the Canadian Journal of Anesthesia.

Clinical question

During your preoperative assessment a 74-yr-old patient informs you that her last operation, a sigmoid colon resection for cancer, was complicated by postoperative confusion. On the evening of the first postoperative day she experienced visual hallucinations and was disoriented to place and time. She states that "she's not been the same" since her surgery. She is more forgetful and has difficulty concentrating. In preparation for her total hip arthroplasty she would prefer a general anesthetic and wants assurance that your anesthetic will not cause further changes in her thinking.

As her upcoming surgery is amenable to either regional or general anesthesia you ask yourself "Does general anesthesia increase the risk of delirium or cognitive dysfunction in the postoperative period?" Seeking an evidence-based answer to this clinical problem you turn to the literature.

Methods

In June 2005 a structured search of MEDLINE from 1966 to present using OVID software was undertaken with the assistance of a reference librarian. Medical subject headings and textwords describing both delirium and postoperative cognitive dysfunction (POCD) were employed (Appendix 1). OVID's Therapy (sensitivity) algorithm was used to maximize the detection of randomized trials while excluding non-randomized research (Appendix 2). One hundred eligible studies were identified using the delirium search strategy: 89 were identified for POCD.

Trials included in this review met the following criteria: enrolled adult patients undergoing non-cardiac surgery; randomly assigned patients to either regional or general anesthesia; and reported at least one measurement of cognitive outcome. Two investigators (GLB and AW) independently reviewed the abstracts of the trials to identify eligible research. The bibliographies of eligible publications were hand-searched to identify trials not identified in the electronic search.

Reviewers abstracted each trial using a standardized Excel spreadsheet (Microsoft Excel 2002, Mississauga, ON, Canada). Details from each study abstracted

included: type of surgery, design of trial, anesthetics compared, outcome (delirium or POCD), outcome measure used; timing of outcome measurement; outcome definition; numbers of patients with postoperative cognitive impairment in regional and general anesthesia groups, primary finding of the study. Trials assessing delirium were those describing delirium, confusion, or using standardized measures of delirium. Trials assessing POCD were those using specific measures of cognitive function. Trials assessing both delirium and POCD were included in both reviews.

The likelihood of methodological bias was assessed using the Jadad score (Appendix 3).¹ The Jadad score assigns points for three key items of trial design: randomization, blinding, and accounting for withdrawals. The maximum possible score is 5. Trials scoring 3 or more are generally considered to be of good methodological quality.

Following abstraction of all methodological information both reviewers assigned a Level of Evidence for each trial using the Centre for Evidence Based Medicine guidelines for Therapy.² This review preferentially cites evidence of the highest quality available and rejects case reports and case control studies when randomized trials were available. Centre for Evidence Based Medicine Levels of Evidence and Grades of Recommendation are described in Appendices 4a and 4b.

Review of current best evidence

Review of abstracts revealed ten eligible trials assessing either delirium or POCD.³⁻¹² Hand search identified an additional 17 articles¹³⁻²⁹ so that a total of 27 articles were reviewed in detail. Seven publications were excluded for using a non-randomized^{18,19,24,27,29} or pseudo-randomized designs.^{23,26} A single trial, published in Japanese, was excluded when a translator could not be identified.⁷ A single systematic review was identified and will be discussed separately.¹² Following review of outcome definitions and measures a total of 18 unique randomized controlled trials were identified: two evaluating delirium; ten evaluating POCD; and six evaluating both. Outcomes for delirium were abstracted from eight trials that enrolled 765 patients (387 regional; 378 general). Outcomes for POCD were identified from 16 trials that enrolled 2,708 patients (1,313 regional; 1,395 general). Key features of included trials are summarized in Tables I and II.

Delirium

Delirium is a transient, fluctuating disturbance of consciousness, attention, cognition, and perception³⁰ that complicates the course of 36.8% (range 0-73.5%) of surgical patients.³¹ Delirium is a harbinger of poor

TABLE I Trials evaluating postoperative delirium

Study	Comparators	n	Jadad	Outcome	CEBM
Berggren, 1987	GA, EA	57	1	11/29 GA <i>vs</i> 14/28 EA “confused” as assessed by the organic brain syndrome scale, $P > 0.05$	2b
Bigler, 1985	GA, SA	40	1	1/20 GA <i>vs</i> 1/20 SA “confused,” $P > 0.05$	2b
Campbell, 1993	GA, RBB	157	2	No group/time interaction on Felix Post Unit Questionnaire, $P > 0.05$	2b
Chung, 1987	GA, SA	44	1	3/24 GA <i>vs</i> 0/24 SA “confused,” $P > 0.05$	2b
Chung, 1989	GA, SA	44	1	2/22 GA <i>vs</i> 0/22 SA “confused,” $P > 0.05$	2b
Cook, 1986	GA, SA	101	2	6/51 GA <i>vs</i> 9/51 SA “confused,” $P > 0.05$	2b
Crul, 1992	GA, SA	60	1	Scores on Hospital Observation List were less favourable in SA patients on POD1, $P < 0.05$	2b
Williams-Russo, 1995	GA, EA	262	3	12/128 GA <i>vs</i> 16/134 EA delirious by DSMIII criteria, $P = 0.50$	1b

GA = general anesthesia; SA = spinal anesthesia; EA = epidural anesthesia; RBB = retrobulbar block; Jadad = Jadad score (maximum score = 5); CEBM = Centre for Evidence Based Medicine Level of Evidence (1a best evidence – 5 expert opinion); DSMIII = Diagnostic and Statistical Manual of Mental Disorders, Third Edition.

TABLE II Characteristics of trials evaluating postoperative cognitive dysfunction

Study	Comparators	n	Jadad	Outcome	CEBM
Asbjorn, 1989	GA, EA	40	1	No group/time interaction on pooled z scores of five tests of cognition, $P > 0.05$	2b
Bigler, 1985	GA, SA	40	1	No group/time interaction on Abbreviated Mental Test, $P > 0.05$	2b
Campbell, 1993	GA, RBB	157	2	No group/time interaction on eight individual tests of cognition, $P > 0.05$	2b
Chung, 1987	GA, SA	44	1	Score on Mini-Mental State less favourable in GA group six hours postoperatively, $P < 0.001$. Otherwise no difference to POD5	2b
Chung, 1989	GA, SA	44	1	No group/time interaction on two individual tests of cognition, $P > 0.05$	2b
Crul, 1992	GA, SA	101	1	No group/time interaction on three individual tests of cognition, $P > 0.05$	2b
Forster, 1990	GA, EA, SA	64	2	No group/time interaction on Mini-Mental State, $P > 0.05$	2b
Fredman, 1998	GA, SA	100	1	Score on Digit Symbol Substitution Test less favourable in GA group 15 min postoperatively, $P < 0.05$. Otherwise no difference to two hours postoperatively	2b
Ghoneim, 1988	GA, SA	91	3	No group/time interaction on 17 individual tests of cognition, $P > 0.05$	1b
Hole, 1980	GA, EA	60	2	8/31 GA <i>vs</i> 1/29 EA noted by investigators to have “mental changes” in hospital, $P < 0.01$ 12/31 GA <i>vs</i> 8/29 EA self-reported “mental changes” following discharge, $P > 0.05$	2b
Jones, 1990	GA, SA	146		Score on Choice Reaction Time less favourable in SA group 90 days postoperatively, $P = 0.04$. Otherwise, no group/time interaction on five individual tests of cognition, $P > 0.05$	2b
Nielson, 1990	GA, SA	64	2	Scores on 31 individual tests of cognition grouped into 12 discrete cognitive abilities. No group/time interaction noted, $P > 0.05$	2b
Rasmussen, 2003	GA, EA, SA	428	3	Scores on seven individual tests of cognition adjusted to control for “learning effect” and converted to z scores. POCD defined as $Z > 1.96$ on two individual tests or on sum of all seven tests. 37/188 GA <i>vs</i> 22/176 RA had POCD on POD7, $P = 0.06$ 25/175 GA <i>vs</i> 23/165 RA had POCD on POD90, $P = 0.93$	1b
Riis, 1983	GA, EA,	30	1	Scores on 13 individual tests of cognition grouped into four discrete cognitive abilities and converted to z scores. No group/time interaction noted, $P > 0.05$	2b
Somprakit, 2002	GA, EA, SA	60	2	No group/time interaction on Thai Mini-Mental State Examination, $P > 0.05$	2b
Williams-Russo, 1995	GA, EA	262	3	No group effect noted on ten individual tests of cognition, $P > 0.005$ corrected for multiple t tests. MCID of ten individual tests of cognition were defined. If test result: less favourable than MCID = -1; within MCID = 0; more favourable than = +1. Plus/minus scores on ten tests added. If -4 or less POCD was diagnosed. Using this definition 5/177 GA <i>vs</i> 7/114 EA had POCD on POD180, $P = 0.50$.	1b

GA = general anesthesia; SA = spinal anesthesia; EA = epidural anesthesia; RBB = retrobulbar block; RA = pooled EA and SA; Jadad = Jadad Score (maximum score = 5); CEBM = Centre for Evidence Based Medicine Level of Evidence (1a best evidence – 5 expert opinion); POD = postoperative day; POCD = postoperative cognitive dysfunction; MCID = minimally clinically important differences.

patient outcome and is associated with increased length of hospital stay,³² greater rates of nursing home placement,³³ and mortality rates approaching 30%.³⁴ Despite the clinical importance of delirium in the perioperative period there has been surprisingly little research on the influence of anesthetic technique on its occurrence.

In seven of the eight trials identified, enrolling a total of 705 patients, the choice of general or regional anesthesia bore no influence on the occurrence of delirium. Only a single trial¹⁷ of 60 patients identified a statistically significant difference in the incidence of delirium/confusion associated with the use of regional anesthesia. In this trial, patients assigned to regional anesthesia experienced less favorable scores of cognitive function on the first postoperative day but were otherwise similar to those assigned to general anesthesia.

Research regarding the influence of anesthetic technique on the incidence of delirium has been further limited by weak research methodology. Of the eight trials reviewed two employed validated tools for the detection and diagnosis of delirium,^{3,11} two relied on institution-specific questionnaires that had not been validated,^{4,17} and the remainder relied on reports of patient behaviour from health care workers and family. In the absence of a formal screening tool both physicians and nurses fail to diagnose delirium in over two-thirds of cases. Indeed, the incidence of delirium was greater in those trials using properly validated assessment tools (11–43%) than in those trials using bedside reports (5–15%). Failure to properly assess and define delirium as an outcome suggests that research in this field is underreporting and/or incorrectly classifying this important event. Furthermore, only a single trial¹¹ scored 3 or more on the Jadad score of methodological bias. It is difficult or impossible to blind both patients and anesthesiologists to the allocation of regional or general anesthesia thus limiting the maximum scores possible. That said, few trials reported randomization methods or patient withdrawals, both factors associated with a reduction in bias.

Within the methodological limitations discussed above the clinician wishing to answer the question “Does general anesthesia increase the risk of delirium in the postoperative period?” can rely on consistent Level 2b evidence from randomized trials to inform their decision. No significant increase in the incidence of delirium associated with general anesthesia was found in the available trials. It is not possible to rule out the possibility of an effect given the relatively small sample size of the available trials and inconsistent surveillance for delirium. More study is required.

Postoperative cognitive dysfunction

Postoperative cognitive dysfunction is a subtle disorder of thought processes that may influence isolated domains of cognition such as verbal memory, visual memory, language comprehension, visuospatial abstraction, attention, or concentration. Postoperative cognitive dysfunction following cardiopulmonary bypass is well described and has now been documented in 25.8% (95% confidence interval 23.1–28.5) of patients one week after non-cardiac surgery.³⁵ Patients demonstrating POCD one week after surgery experience a decline in their activities of daily living³⁵ and quality of life³⁶ following hospital discharge and are nearly three times as likely to suffer cognitive decline one to two years postoperatively (odd ratio 2.84; 95% confidence interval 1.35–5.96).³⁷

If research on postoperative delirium can be faulted for not using validated assessment tools then research on POCD can perhaps be accused of using too many assessment tools. Studies identified in this review used anywhere between one and 31 individual tests of cognition. Most of these tests are subsets of test banks used for the assessment of memory and intelligence in adults. Few of the tests employed define a score at which a given patient can be said to be impaired. For this reason only three trials^{9,11,22} quoted rates of POCD ranging from 15–25% in-hospital and 5–10% following discharge. Instead, most trials report mean scores for each individual test at varying times, then assess differences between points-in-time and between groups using analysis of variance.

Only a single trial²² of 60 patients identified a statistically significant decline in cognitive outcome associated with general anesthesia. This trial used no test of cognitive function but instead relied on a bedside clinical assessment of the patient’s “mental status” by the investigators and family members. When patients were assessed following discharge from hospital there was no difference in cognitive outcome between regional and general anesthesia. The remaining 15 trials detected a decrease in cognitive scores in the immediate postoperative period followed by steady improvement in scores that often exceed baseline assessment by hospital discharge. This change in scores over time is referred to, in statistical terms, as a within-group effect. It should be noted that the improvement in scores seen might reflect the characteristics of the test used rather than an improvement in the patient’s cognitive abilities *per se*. Few cognitive tests are designed for repeated testing and many patients score better on them with practice, a so-called learning effect. Despite the significant within-group effect noted, the choice of anesthetic technique was associated neither with a significant dif-

ference in scores overall (a between-groups effect) nor with a significant difference in scores at any given time point (group-time interaction). When the math is said and done it is apparent that there is no statistically significant difference in cognitive outcome associated with the choice between regional and general anesthesia.

Similar to the findings in delirium research, trials assessing POCD suffered from a lack of blinding and scored relatively poorly on the Jadad score. Only three of the 16 trials reviewed scored 3 or greater^{9,11,20} but these three trials provide consistent Level 1b evidence suggesting that the choice of regional or general anesthesia bears no impact on the occurrence of POCD.

Unlike delirium research, POCD has been the subject of a systematic review.¹² Conducted in 2003, this systematic review identified 19 randomized controlled trials and four observational studies. Only one of 19 randomized trials²² and none of the observational trials in this systematic review reported a statistically significant difference in cognitive outcomes with regional anesthesia. In comparison, this evidence-based clinical update limited itself to randomized controlled trials, excluded four trials using non- or pseudo-random allocation methods, and included one French-language publication. The variety of outcome measures employed precluded statistical pooling of the results (meta-analysis) but the qualitative results of this systematic review are consistent (homogenous) and can be graded as Level 1a evidence.

After reviewing the statistics and available data, the clinician wishing to answer the question “Does general anesthesia increase the risk of POCD in the postoperative period?” can rely on consistent Level 1 evidence from a systematic review and three randomized controlled trials, as well as Level 2b evidence from 13 other randomized trials, to inform their decision. Best available evidence indicates that the choice between regional and general anesthesia bears no statistically significant influence on the likelihood of postoperative POCD.

Conclusions

Delirium and POCD are common complications among patients undergoing anesthesia and surgery. Prevention and treatment of postoperative cognitive outcomes are challenges for the anesthesiologist interested in perioperative medicine. Review of the best available evidence, from systematic review and randomized controlled trials, suggests that general anesthesia is not associated with a statistically significant influence on the occurrence of cognitive change following surgery. What other factors might play a role in postoperative cognitive outcomes?

Increasing age predicts both delirium³⁸ and POCD³⁵ suggesting that older patients may have pre-existing conditions or limited reserve to cope with the physiological challenges of anesthesia and surgery. A relationship between physiological stress and cognitive change is suggested by studies that frequently identify delirium and POCD following major/complicated surgery^{35,38} but note it rarely following minor ambulatory surgery.³⁹ Unfortunately none of these characteristics can be modified by the anesthesiologist. Could selection of drugs used in the perioperative period play a role?

While the pathophysiology of delirium is incompletely understood it likely involves relative decreases in muscarinic cholinergic activity, increases in dopaminergic activity, or some combination of both.⁴⁰ A cholinergic model is supported by observational research in hospitalized elders that demonstrates a nearly twofold increase in the risk of delirium in patients exposed to diphenhydramine, a drug with well known anticholinergic properties.⁴¹ Less still is known about the pathophysiology of POCD; however, failure of cholinergic neurotransmission is also felt to be central to the mechanism of other cognitive disorders such as Alzheimer’s disease and vascular dementia.⁴² Pharmacologic management strategies based on central cholinergic and dopaminergic neurotransmission await future prospective trials.

Review of the existing literature on anesthesia and cognitive outcomes suggests that investigators conducting these future trials must improve their methods. Simple, validated tools for the assessment of delirium are available for use in both ward⁴³ and intensive care⁴⁴ settings. The work of the International Study of Perioperative Cognitive Dysfunction⁴⁵ and consensus recommendations for the assessment of cognition following cardiac surgery^{46,47} should be reviewed by investigators interested in POCD. Going forward, investigators should develop a standardized suite of assessment tools, analysis methods that correct for multiple comparisons and learning effect, and an agreed-upon definition of POCD.

Recommendations

Returning to our patient you can offer her only limited reassurance. The patient can be told that she is not unique in her experience, as both delirium and POCD are relatively common occurrences following anesthesia and surgery. You can provide a Grade B recommendation based on consistent Level 2b evidence that the choice between general anesthesia and regional anesthesia for her procedure has not been associated with an increased risk of developing post-

operative delirium. Furthermore, you can provide a Grade A recommendation based on consistent Level 1a and 1b evidence that her choice will not influence her likelihood of developing further lasting changes in her memory and concentration. Unfortunately, a more satisfying answer, with evidence-based prophylaxis and treatment options for postoperative cognitive outcomes, awaits further research.

APPENDIX 1 Literature search

Database: OVID MEDLINE(R) <1966 to June Week 4 2005>

Search strategy:

1. exp ANESTHESIA/ (109722)
2. exp Cognition Disorders/ (25276)
3. postoperative cognitive dysfunction.mp. (55)
4. 2 or 3 (25282)
5. 1 and 4 (128)
6. limit 5 to "therapy (sensitivity)" (89)
7. from 6 keep 1-89 (89)

Database: OVID MEDLINE(R) <1966 to June Week 4 2005>

Search strategy:

1. exp ANESTHESIA/ (109722)
2. exp DELIRIUM/ or delirium.mp. (13488)
3. delirious.mp. (534)
4. 2 or 3 (13663)
5. 1 and 4 (123)
6. limit 5 to "therapy (sensitivity)" (100)
7. from 6 keep 1-100 (100)

APPENDIX 2 OVID Limit "Therapy (Sensitivity)"

1. randomized controlled trial.pt.
2. dt.fs. [dt=drug therapy]
3. tu.fs. [tu=therapeutic use]
4. random\$.tw.
5. or/1-4

APPENDIX 3 Jadad score

Please read the article and try to answer the following questions:

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items:

Either give a score of 1 point for each "yes" or 0 points for each "no." There are no in-between marks.

Give 1 additional point

If for question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.)

and/or:

If for question 2, the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:

If for question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or:

For question 2, the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet *vs* injection with no double dummy)

Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clinical Trials* 1996; 17: 1-12.

APPENDIX 4a Levels of evidence for studies about therapy or harm

Level Study design

1a	Systematic review of RCTs (with homogeneity)
1b	Individual RCT (with narrow confidence intervals)
1c	All or none study
2a	Systematic review of cohort studies (with homogeneity)
2b	Individual cohort study
2c	Poor quality RCT
3a	Outcomes research
3b	Ecological survey
4	Systematic review of case-control studies (with homogeneity)
5	Individual case-control study
6	Case-series
7	Poor quality cohort study
8	Poor quality case-control study
9	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

RCT = randomized controlled trial. Adapted from Oxford-Center for Evidence Based Medicine. Levels of Evidence and Grades of Recommendation. Available from URL; http://www.cebm.net/levels_of_evidence.asp#notes.

APPENDIX 4b Grades of recommendation

Grade	Level of evidence
A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies
C	Extrapolations from Level 1 studies
D	Level 4 studies
E	Extrapolations from Level 2 or 3 studies
F	Level 5 evidence
G	Troublingly inconsistent or inconclusive studies of any level

Extrapolations – data used in a situation with clinically important differences from original study population. Adapted from Oxford-Center for Evidence Based Medicine. Levels of Evidence and Grades of Recommendation. Available from URL; http://www.cebm.net/levels_of_evidence.asp#notes.

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