

Information in practice



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BMJ 2003;327:266-9

What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes

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Abstract

Objective To evaluate systematically the review literature on type 2 diabetes to assess transmission of the findings of the United Kingdom prospective diabetes study (UKPDS), an important source of recent valid patient oriented evidence that matters (POEMs).

Design Inception cohort analysis of the recent medical literature.

Studies reviewed Thirty five reviews on treatment of type 2 diabetes.

Main outcome measures Presentation of three types of information from UKPDS in review articles: recommendations based on patient oriented outcomes of study; recommendations contradicted by patient oriented outcomes of study; and recommendations based on disease oriented outcomes for which no patient oriented evidence exists.

Results Only six of the reviews included the POEM that tight blood glucose control had no effect on diabetes related or overall mortality. Just seven mentioned that metformin treatment was associated with decreased mortality. Most (30) of the reviews did not report that diabetic patients with hypertension benefit more from good blood pressure control than good blood glucose control. No review pointed out that treatment of overweight patients with type 2 diabetes with insulin or sulphonylurea drugs had no effect on microvascular or macrovascular outcomes. Thirteen reviews recommended drugs as first line treatment for which we do not have patient oriented outcomes data. The average validity assessment score was 1.3 out of a possible score of 15 (95% confidence interval 0.9 to 1.8).

Conclusions Review articles on the treatment of type 2 diabetes have not accurately transmitted the valid POEM results of the UKPDS to clinicians. Clinicians relying on review articles written by experts as a source of valid POEMs may be misled.

Introduction

“Information mastery” involves the ability to identify, evaluate, and apply valid and relevant information quickly.¹ It is based on the concept that information has different degrees of usefulness, and that the best information is highly valid, highly relevant, and takes little work to locate, evaluate, and understand. Validity is a

matter of satisfying the criteria developed by the Evidence-Based Medicine Working Group.² Relevant information is called “patient oriented evidence that matters” (POEMs).³ Patient oriented evidence tells clinicians, directly and without the need for extrapolation, that a diagnostic, therapeutic, or preventive procedure helps patients live longer or live better. This information matters when it requires a change in practice of a clinician.

Patient oriented evidence is contrasted with “disease oriented evidence” (DOE), which is research focusing on either intermediate or surrogate outcomes.⁴ Many practices in medicine are currently based on disease oriented evidence, which may later be shown to be either correct or incorrect when the patient oriented outcomes are studied. Numerous examples exist of medical practice based on disease oriented evidence that have been shown, after the publication of truly patient oriented evidence, to be not only ineffective but even harmful.⁵ On the other hand, new, valid POEMs often are rejected, especially when they don’t “make sense” or conflict with disease oriented evidence.

Although valid POEMs are usually found in research articles, most clinicians rely on expert recommendations on which to base their clinical care.⁶ These recommendations are transmitted via review articles, book chapters, continuing medical education presentations, consensus conferences, and consensus guideline development.

These recommendations can be supported either by patient oriented evidence, disease oriented evidence, or some combination of preliminary research findings augmented with expert opinion. We sought to measure the accuracy of one mode of information dissemination by evaluating how experts represented the results of the United Kingdom prospective diabetes study (UKPDS).⁷⁻¹⁰

The United Kingdom prospective diabetes study (UKPDS)

Started in 1977, the UKPDS was designed to determine whether tight glycaemic control decreases diabetes related complications and increases life expectancy. A sub-study within the main study investigated whether tighter control of blood pressure in patients with hypertension decreased complications (see bmj.com). The UKPDS provided several outcomes that can be categorised as POEMs (see table).



The review articles evaluated in this study (w1-w40) are listed on bmj.com

Outcomes of the United Kingdom prospective diabetes study (UKPDS) and their subsequent reporting in 35 review articles on treatment of type 2 diabetes

Results	Reported in reviews	
	No of reviews	Percentage (95% CI)
Patient oriented evidence that matters (POEMs)		
Tight control (fasting blood glucose <6 mmol/l) did not prevent premature mortality (17.9 v 18.9 deaths per 1000 patient years, P=0.44)	6	17.1 (4.5 to 29.8)
In overweight patients, treatment with metformin decreased mortality related to diabetes or other cause (13.5 v 20.6 events per 1000 patient years, P=0.021. NNT per year=141 (95% CI 115 to 183))	7	20.0 (6.6 to 33.4)
In overweight patients, metformin significantly decreased diabetes related outcomes (29.8 v 43.3 events per 1000 patient years, P=0.0034. NNT per year=74 (63 to 90))	14	40.0 (23.5 to 56.5)
Tight blood pressure control decreased diabetes related mortality (13.7 v 20.3 events per 1000 patient years, P=0.019. NNT=152 (122 to 201))	10	28.6 (13.4 to 43.8)
Tight blood pressure control decreased complications (50.9 v 67.4 events per 1000 patient years, P=0.0046. NNT per year=61 (57 to 74))	17	45.7 (29.0 to 62.5)
β blocker atenolol, as initial treatment, had similar effects on complications as ACE inhibitor captopril (P=0.28)	7	20.0 (6.6 to 33.4)
Control of blood pressure had greater effect on complications than blood glucose control (24% v 12% decreased risk in diabetes related complications)	5	14.2 (2.5 to 26.0)
In overweight patients treatment with insulin or sulphonylureas had no effect on individual or aggregate microvascular or macrovascular outcomes (36.8 v 38.9 events per 1000 patient years)	0	
Quality of life not affected, positively or negatively, by tight blood glucose control	0	
Disease oriented evidence		
Tight control of blood glucose decreased likelihood of patients experiencing any of 21 different complications (40.9 v 46.0 events per 1000 patient years, P=0.029. NNT per year=196 (153 to 272))	28	80.0 (66.6 to 93.4)
Tight blood glucose control had no effect on any individual macrovascular complication	10	28.6 (13.4 to 43.8)
Almost all the benefit on complications was due to reduced need for photocoagulation. Eliminating this outcome measure eliminated all of the benefit seen in the trial ¹³	1	2.9 (0 to 8.5)
Although photocoagulation rates were less, there was no effect on vision loss with tight control (2.9% v 3.5%, P=0.39)	1	2.9 (0 to 8.5)
Weight gain occurred in all patients except those treated with metformin (average 3.1 kg)	18	51.4 (34.6 to 68.2)
Changes in HbA _{1c} did not correlate with treatment outcomes (HbA _{1c} =7.0% in intensively treated group v 7.9% in conservatively treated group)	2	5.7 (0 to 13.5)
Issues for which no patient oriented evidence exists		
Drugs that have equivalent effect on HbA _{1c} have equivalent effect on complications or outcomes (in UKPDS only metformin, in overweight patients, decreased mortality and morbidity)	7	20.0 (6.5 to 33.4)
α glucosidase inhibitors, thiazolidinediones, nateglinide, and repaglinide can be used as first line drugs (not studied in UKPDS, no patient oriented evidence reported)	13	37.1 (20.1 to 53.4)
Role of self monitoring in patients with type 2 diabetes (self monitoring was used in UKPDS only in patients requiring at least 12 units of insulin)	11	31.4 (15.8 to 47.0)

NNT=number needed to treat. ACE inhibitor=angiotensin converting enzyme inhibitor. HbA_{1c}=haemoglobin A_{1c}.

Methods

Search strategy

To evaluate the selection and transmission of the results of the UKPDS, we assembled a convenience sample of review articles. We searched Medline, the *Cochrane Library*, the *Turning Research into Practice (TRIP)* database, *Bandolier*, and *MD Consult*. We also searched four controlled circulation journals with online contents. The search was not designed to be exhaustive but to be a realistic representation of expert written reviews available to many practising clinicians.

Inclusion criteria

We included articles if they were reviews (including systematic reviews and meta-analyses), commentaries, structured reviews, or book chapters published in English focusing on the treatment of patients with type 2 diabetes. We excluded editorials; drug monographs; articles dealing primarily with the pathophysiology, screening, or diagnosis of diabetes; reviews focusing on non-drug treatments; and reviews of treatment of type 2 diabetes restricted to children or adolescents.

Evaluation of reviews

We evaluated each article for validity using a scoring system of strict¹¹ and looser¹² criteria of validity (see *bmj.com*), weighting the scoring system to focus on the most crucial elements. We piloted these criteria on review articles on other topics and were able to use them to separate reviews into three categories: systematic reviews (score ≥ 10); evidence based reviews (score 5-9), and expertise based reviews (score < 5).

To determine the flow of information, we evaluated the review articles to document the presentation of three types of information: recommendations based

on the patient oriented outcomes of the study, recommendations contradicted by the patient oriented outcomes of the study and recommendations based on disease oriented outcomes for which no patient oriented evidence exists.

Results

From our literature search we identified 436 reviews published between November 2000 and May 2002. We found six online book chapters in *MD Consult* and 257 page hits to diabetes in four non-indexed controlled circulation journals with online contents. After removing reviews that did not meet our inclusion criteria and five reviews that did not present any results from the UKPDS, we analysed the content of 35 review articles of type 2 diabetes.

Based on academic affiliation, most (30/35) of the reviews were "academic summary reviews"¹³ written by endocrinologists for non-endocrinologists. The mean validity score for the 35 papers was 1.3 out of possible score of 15 (95% confidence interval 0.9 to 1.8). None of the reviews would have met the criteria set forth by the Evidence-Based Medicine Working Group to be considered a valid systematic review.¹¹ With the less rigorous criteria,¹² the reviews, on average, fulfilled only 13% of the requirements (average score 1.2 out of a possible 9 (95% confidence interval 0.8 to 1.6)).

Presentation of patient oriented evidence that matters

The finding that tight glucose control does not change overall mortality or diabetes related mortality was mentioned in only six of the 35 reviews. One reviewer explained that the lack of effect could have been due to

an insufficient effect on haemoglobin A_{1c}, too short a study period, or that, despite discussing mortality, “the end-points measured were not sufficiently sensitive.”¹³

Only 14 of the reviews mentioned the effect of metformin on diabetes related outcomes in overweight patients. Twenty eight reviews failed to inform readers that metformin was the only drug associated with decreased mortality.

Almost half (17) of the reviews did not mention the need for blood pressure control in patients with diabetes. Only five reviewers pointed out that diabetic patients with hypertension benefit more from blood pressure control than blood glucose control. Only seven of the reviews pointed out the finding that angiotensin converting enzyme inhibitors and β blockers, as starting drugs for controlling hypertension, were equivalent.

Disease oriented evidence

Most of the reviews (28) mentioned that tight control of blood glucose decreased the aggregate outcome of 21 complications. However, only one reviewer pointed out that much of this aggregate decrease could be attributed to changes in the surrogate outcomes of less change in serum creatinine concentration and a decreased need for photocoagulation, without any difference between the groups in vision loss or need for dialysis. No reviewer pointed out that treatment with insulin or sulphonylurea drugs had no significant effect on microvascular or macrovascular outcomes in overweight patients, the group most commonly encountered in clinical practice.

Seven reviews reported the weaker epidemiological analysis relating decreased haemoglobin A_{1c} to decreased complications,¹⁴ using this analysis to support a conclusion that HbA_{1c} should be as low as possible for all patients regardless of the methods used to do so. No reviewer mentioned that lowering HbA_{1c} with drug treatment was not associated with a significant benefit in the intention to treat analysis of the randomised study.

Issues for which no patient oriented evidence exists

Several hypoglycaemic agents are marketed that were not studied in the UKPDS. Currently there are no patient oriented outcomes data available to support their use in treating patients with type 2 diabetes. However, 13 of the reviews recommended drugs without POEM data as first line treatment, and seven stated that drugs that have an equivalent effect on HbA_{1c} were interchangeable.

Discussion

We found that the results of the most important research in diabetes in the past 25 years were incompletely and often inaccurately transmitted to readers. The extent to which these mainly non-systematic reviews have changed clinical practice is unknown, but reviews are one of the typical ways new information is transmitted to clinicians. Thus, our results have far reaching implications for how the current medical information system transmits new research results from academia to practitioners.

The lack of effect of tight blood glucose control on mortality was not reported by 83% of the reviewers, and none of the reviewers reported that neither treat-

What is already known on this topic

Review articles, especially if they are not systematic in their approach, can present incomplete or incorrect information, with few clues given to unsuspecting readers

Previous research has indicated that the quality of a review article varies inversely with the expertise of the author

What this study adds

The results of the United Kingdom prospective diabetes study have not been transmitted accurately via review articles

Much of the “patient oriented evidence that matters” from the study is missing from these reviews

Clinicians relying on these information sources for accurate clinical information may be misled

ment with insulin nor sulphonylureas affected microvascular or macrovascular complications of diabetes in overweight patients.^{15 16} Only five of the reviewers mentioned the greater impact of blood pressure control in patients with diabetes who also have hypertension. A subsequent analysis of preventive measures in patients with diabetes found that control of cholesterol and blood pressure have a significantly greater effect on mortality and complications than tight glucose control.¹⁷

Many recommendations did not take into account the result, shown in the randomised aspect of the UKPDS, that changes in haemoglobin A_{1c}, a marker of long term blood glucose control, had no impact on the morbidity or mortality associated with diabetes. Instead, several reviews, including that by the American Diabetes Association, chose to focus on the observational data provided in a subsequent analysis by Stratton.¹⁴ Treating this controlled trial as an epidemiological study may be illusory¹⁸ and reflects the preconceptions of the reviewers.¹⁵ The newly found neutral or negative effect of hormone replacement therapy to decrease cardiovascular disease, which was thought to be beneficial based on population studies, is the latest example of the hazards of this type of research. The intention to treat (that is, randomised) results of the trial did not show a substantial benefit from reducing HbA_{1c} levels and is a better indicator of the true impact of drug treatment. No reviewer discussed the methodological problems with the non-randomised analysis.

Conclusion

The current system of transmitting new research to clinicians by means of reviews is less than optimal, at least for new important research in type 2 diabetes. Many of the reviews in our analysis did not provide the valid POEMs or identify the level of evidence supporting the reviewers’ recommendations. Instead, the recommended first line treatments for type 2 diabetes seem to be based on pathophysiological reasoning rather than patient oriented outcomes data.¹⁹ Much of the

advice given by reviewers is either based on valid disease oriented evidence or on non-valid POEMs. In contrast, this advice can be called "prescriptive recommendations based on substandard evidence" (PROSE).

Basing clinical practice on PROSE is not necessarily harmful unless it is contradicted by evidence from valid POEMs. Useful tools for clinicians wanting to find the best information to answer their clinical questions should, instead of providing PROSE, present recommendations with the level of evidence clearly identified for readers who must know whether the information is based on POEMs, disease oriented evidence, or the experience of the writer. Well informed and open minded clinicians can then improve their patient management and the lives of their patients as valid POEMs replace lower level evidence.

We thank Laurie Schwing for her help with the literature search. Contributors: see bmj.com.

Funding: Partial funding to support this project was obtained from the PinnacleHealth System Foundation.

Competing interests: Both authors hold stocks in InfoPOEMs and receive royalties from the sale of InfoRetriever and InfoPOEMs.

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(Accepted 1 April 2003)

Commentary: The faults of expert reviews are already well known

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The authors are well known proponents of evidence based medicine and introduced the concept of patient oriented evidence that matters (POEMs) and disease oriented evidence in the early 1990s. The current study claims that the two main POEMs from the United Kingdom prospective diabetes study (UKPDS), namely that for patients with type 2 diabetes blood pressure control is more important than glycaemic control and that metformin should be first line therapy, are not well presented in review articles. It is odd, therefore, that they choose a "convenience sample" of review articles rather than undertaking a systematic review. Thus the search strategy is broad, and it is hard to claim that using the authors as reviewers is an independent process.

Having said this, the point is well made that review articles, particularly those written by specialists, tend to be of dubious value, with authors selectively choosing evidence to support their own prejudices. I would argue, however, that most practising clinicians know this already, and my experience is that most UK primary care physicians are aware of the key messages, or POEMs, as described above. My perception, albeit limited, is that the experience of a patient with type 2 diabetes is much more likely to include metformin treatment, intensive blood pressure monitoring and control, and intensive management of dyslipidaemia than the historical reliance on

haemoglobin A_{1c}. This has happened despite the apparent dissemination of misleading information described by the authors.

The paradox of using non-evidence based methods to discredit non-evidence based reviews is striking, and is similar to using a lecture method to impart the information that lectures are not the best method for disseminating information. If one were to apply information mastery to the current paper one would not get past the abstract (some would suggest the title). The message is important, however, that expert reviews cannot be trusted. Sackett has always been wary of experts and has recommended that once a person has become an expert he or she should change jobs. This information has obviously filtered through to the "coal face" as clinicians are acting much more on primary data than filtered expert opinion.

The goal of the authors, to effect change through clinical research using clinically important end points rather than intermediate or "proxy" measures, seems to me to have been achieved despite rather than because of the dissemination of poor information described. We should perhaps question why these expert reviews continue to be published, given both their lack of rigour and their apparent lack of influence.

Competing interests: None declared.

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