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Letters to the Editors

Cabergoline vs. Levodopa Monotherapy

We question the conclusion of Smala and colleagues[1] that cabergoline is cost-effective compared to levodopa monotherapy (LD) for patients 60 years of age or older with early Parkinson's disease (PD). There are several important methodological deficiencies in their report: (1) The analysis is not based on a properly randomised comparison. Instead, only a selected subset of the patients entered into the PKDS009 trial[2] is analysed. There is a substantial imbalance in the numbers in each arm (110 LD and only 76 cabergoline), because patients in the cabergoline arm who had LD added are excluded. Presumably, in many cases, LD was added because cabergoline was failing to control the symptoms of PD adequately. Thus, the remaining cabergoline-only patients will represent a highly selected group of patients with less severe disease who cannot be meaningfully compared with the unselected LD group. No conclusions about cost-effectiveness can be drawn from such a biased comparison.

(2) Further bias is introduced by selective post hoc emphasis on the over age 60 subgroup — seemingly because these were the most favourable results for cabergoline. The main trial report[2] did not analyse the patients separately by age group, suggesting that the separate analysis by age <60 years and ≥ 60 years was not a prespecified subgroup analysis. Therefore, the unanticipated selective benefit in older patients is very likely to be a chance "false-positive" finding. Inappropriate interpretation of unanticipated apparent subgroup effects is one of the biggest problems in the medical literature[3] and can easily lead to misleading, often unduly positive, impressions of treatment efficacy.

(3) A further serious problem is that there is no indication of whether the efficacy differences used as the basis for the cost-effectiveness analysis are statistically significant, as no *P* values or confidence intervals (CI) are given for any of the estimates. Thus, the reader has no idea of the degree of uncertainty surrounding the reported costs; therefore, it is meaningless to state, for example, that the "costs for each motor complication-free patient reached €104,400 for patients <60 years of age." For illustrative purposes, we have performed some crude calculations (it would be helpful if the authors could provide the actual figures). The main PKDS009 trial[2] report gave a *P* value of <0.02 for the difference in time to onset of motor complications, with 47 and 70 patients in the cabergoline and levodopa arms, respectively, developing complications. This finding equates to a hazard ratio of approximately 0.65, with 95% CI 0.45 to 0.93, and an absolute risk reduction of approximately 14% (consistent with the plot in Rinne and colleagues[2]), with 95% CI of 22% to 3%. From this finding, the point estimate for the number needed to treat (NNT) to avoid one motor complication is 8, but the CI ranges from 5 to 33. Importantly, the CI for NNT is not symmetrical, and as the upper limit approaches the point of no effect, the NNT increases rapidly. Thus, the overall costs could be more than fourfold higher than the point estimate at one end of the scale, but only approximately half as much at the other. Furthermore, the smaller numbers in each age subgroup mean that the CIs will be wider within each, leading to even greater uncertainty. Given these uncertainties, cost-effectiveness for cabergoline over LD cannot be claimed.

(4) Another criticism of the study is the emphasis on motor complications and clinician-based rating scale. The UPDRS does not fully reflect patients' own perceptions of their functioning and quality of life. Other factors also need to be taken into account. For example, the main report on the PKDS009 trial[2] shows that, on balance, side effects are worse with cabergoline, and, in particular, there is a 6% excess of serious adverse events with cabergoline. These adverse effects need to be balanced against beneficial effects on the symptoms of PD. The most appropriate outcome to achieve this is patient-rated quality of life using a well-validated disease-specific questionnaire such as the PDQ-39.[4] This approach can be combined with health economic analysis to provide an estimate of cost-effectiveness.

(5) Considerable concern has been expressed recently about, the impact of commercial funding on the results of trials, e.g., "systematic bias favours products which are made by the company funding the research"[5] and "scientific studies can be manipulated in many ways to give results favourable to companies."[6] We note that the study by Smala and coworkers was supported by the company that manufactures cabergoline. It seems particularly important that such commercially funded research, particularly when making strong claims of benefits for the company's product, should be subject to more rigorous statistical refereeing than appears to have been the case for this seriously flawed study.

Finally, we do at least agree with the conclusion of Smala and colleagues that "further large clinical trials are needed to evaluate the efficacy and cost-effectiveness of treatment options in Parkinson's disease." These should be academic investigator-led studies, designed and conducted independently of any commercial interests, such as the current PD MED trial in the UK (online at http://www.pdmed.bham.ac.uk), which is funded by the UK NHS Health Technology Assessment programme.

Conflict of interest: We are investigators in the PD MED trial and, thus, have a vested interest in obtaining objective evidence on the best treatment for PD. C.E.C. has received honoraria for lectures, consultancy fees, and travel expenses from the manufacturers of many of the drugs used to treat PD.

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Reply: Cabergoline versus Levodopa Therapy

We thank Wheatley and colleagues for their interest in our work. They raise important points with regard to the interpretation of modeling studies, particularly with regard to our recent publication.[1] Decision–analytic modeling is a complex approach that can be used for extrapolating available data from clinical trials, for integrating data from different sources, and for combining clinical and economic evidence. Ideally, a decision analysis includes effects that occur in a naturalistic setting and answers questions about long-term outcomes that could not be observed in randomized clinical trials.[2] In most cases—if not always—a decision model reflects a simplification of reality and rests on various clinical, epidemiological, and economic assumptions. The results are not meant to replace the clinician's expertise nor the societal decision-making process. But when they are interpreted carefully, a decision model can offer valuable aids to decision making.[3]

As described in the publication, our decision analysis was based on clinical data from a subsample of the cabergoline trial "Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications" (PKDS009).[4] We excluded patients who required additional levodopa during the study period. Although, from an a priori perspective, the argument that patients excluded from the cabergoline arm represent those with more severe disease seems to be clinically plausible, the empirical data do not support this hypothesis. To test for difference in severity of Parkinson's disease (PD), we compared Unified Parkinson's Disease Rating Scale (UPDRS) III scores of the cabergoline monotherapy group with those of the cabergoline plus levodopa group. There was no statistically significant difference between patients in the two arms who needed levodopa (mean UPDRS III, 11.1 $\pm$ 8.6) compared to those with cabergoline alone (mean UPDRS III, 12.2 $\pm$ 11.5), and even the direction of this difference did not support the above hypothesis. Furthermore, we did not (as Wheatley and colleagues suggest) selectively exclude patients with additional levodopa only from the cabergoline arm. Instead, we also excluded those patients from the levodopa arm who received an increased levodopa dosage compared to their baseline dosage. Therefore, it is unlikely that our subgroup analysis is biased in a systematic way.

Contrary to the description of Wheatley and coworkers, our age-specific analysis was part of the study protocol and the cutpoint of 60 years was set a priori. The rationale for an age-specific analysis was that treatment recommendations at the time the study was conducted called for the use of dopamine agonists as first-line therapy in patients 55 to 60 years of age, whereas levodopa was recommended in patients over 70 years of age.[5] As in our prospective economic study, most patients aged 60 to 70 years were initially treated with levodopa, we defined two treatment groups: patients with <60 and ≥ 60 years. As Wheatley and colleagues correctly point out, the main trial report did not provide subgroup analysis by age. Particularly with regard to complication rates, the number of events was too small to allow for any meaningful subgroup analyses. We, therefore, did not (as suggested by Wheatley and colleague's comments) use age-specific complication probabilities in our model, but assumed constant complication probabilities across age, time, and also Hoehn & Yahr stages, and in fact highlighted this explicit assumption in our publication (see sections *Results* through *Complication Events*). Only UPDRS scores and excess mortality were modeled as age-dependent (see Tables 2 and 3 in our publication). We transformed probabilities (P) for t years into rates (r), using the formula $P = 1-\exp(-r \times t)$, and then transformed rates into 1-year probabilities.[6] This strategy resulted in complication probabilities of 0.01 per year for cabergoline monotherapy (4 of 76 patients during 5 years) and 0.03 for levodopa (17 of 110 patients during 5 years).

We appreciate the suggestion of Wheatley and coworkers of a number needed to treat (NNT) calculation, including an uncertainty analysis and present one here. For the 5-year time horizon, we derived a relative complication risk of 0.34 (95% confidence interval [CI], 0.12 to 0.97) and an absolute risk reduction of 10% (95% CI, 2% to 19%) when comparing cabergoline monotherapy with levodopa in the subsample. This approach translates into a NNT to avoid one complication of 10 (95% CI, 5 to 50). As correctly expected by Wheatley and colleagues, the 95% CI for NNT is both asymmetrical and wider than the 95% CI derived from the entire study sample. This calculation underscores from the NNT perspective what

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we discussed in our study: the main limitation of our study is the limited sample size of the analyzed subgroup. In our study, we emphasized the need for further trials with larger sample size. This conclusion is supported by the results of the NNT analysis. However, as decisions must be made regarding therapy for current patients, we made the best use of the current evidence. This use is, of course, subject to change when new data become available.

We disagree with the statement by Wheatley and coworkers that uncertainty is a reason for not claiming cost-effectiveness. Quite the contrary, we believe that decision analysis is a suitable tool for evaluating decisions that must be made under uncertainty.[7,8]

We completely agree with Wheatley and colleagues that any clinical scale measures only part of patients' perceptions of a disease and do not reflect their entire health-related quality of life, and in fact, explicitly discussed this issue in our study (p. 904). However, there are several reasons that we disagree with the use of the disease-specific questionnaire PDQ-39: (1) motor complications have only a minor impact on health-related quality of life as measured by PDQ-39[9,10]; (2) 58% of observed variation in PDQ-39 is defined by Hoehn & Yahr stage and depression (Becks' Depression Index)[11]; and (3) PDQ-39 does not reflect patient preferences (utilities) and, therefore, is of limited use in economic evaluations.[12] Instead, we suggest the development of an algorithm that transforms UPDRS scores into patient preferences, e.g., measured with a generic utility index such as EuroQol (EQ-5D). We recently have completed such work for German patients,[13] and we will apply this algorithm in our future PD models for the context of the German health care system. In this context, we would also like to draw the attention to a recent study published by Lindgren and colleagues, who also evaluated the costs of cabergoline but included quality-adjusted life years.[14] We used the UPDRS rating scale for assessment of efficacy because it is commonly used in both clinical practice and studies and, therefore, facilitates comparability across different cost-effectiveness studies.

Wheatley and coworkers point out an important issue concerning the impact of commercial funding on the results of clinical trials. Although our analysis is not a clinical trial but a cost-effectiveness study, we think the same concern should be raised for this study type. However, we do not agree that third-party funded research is equal to an "a priori" systematic bias to favor a certain commercial product. Our study was funded by unrestricted grants of the German Federal Ministry for Education and Research (BMBF) and Pharmacia Corporation (Kalamazoo, MI). The grant sponsors had no input into study design, data analysis, manuscript preparation, or decisions to submit the paper for publication. We think that an explicit and transparent documentation of the decision model and all input parameters is one of the best ways to facilitate the referee's rigorous assessment of model quality and statistical issues.[15] Following this policy, we laid out the structure of the Markov model (Fig. 1) as well as all model input parameters and calculations (Tables 2 and 3).[1]

Finally, we agree that a concise evaluation of any health technology of relevant public health impact should be addressed in a detailed health technology assessment (HTA), including clinical, quality-of-life, economic, and cost-effectiveness aspects, as well as ethical, legal, and other nonquantifiable issues (see International Network of Agencies for Health Technology Assessment, online at http://www.inahta.org). Such an HTA should include and compare several pharmaceutical and surgical PD treatments. Therefore, we recommended the evaluation of treatment for PD earlier this year for the priority list of the HTA program of the German Agency for Health Technology Assessment (DAHTA) at the German Institute for Documentation and Information (DIMDI)/ German Federal Ministry of Health and Social Security. Although some may argue that studies commissioned by academic, HTA, or government institutions are associated with their own bias, we hope—in accordance with Wheatley and colleagues—that this likelihood is small.

In general, to avoid bias or manipulation of scientific studies—independent of whether this study is a driven by academia or a third party—data (and not only results) of such research should be available and accessible to the scientific community. One important step toward more transparent research is the evaluation projects that Clarke and coworkers have initiated in the United Kingdom and that we have initiated within the German Competence Networks on Parkinson's disease.

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Re: Cabergoline versus Levodopa Monotherapy: A Decision Analysis

I read with interest the cost-effectiveness analysis of Smala and colleagues[1] comparing cabergoline to levodopa monotherapy. The authors estimated the cost of cabergoline monotherapy per motor complication prevented or per one-point improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) over 10 years using data from both a clinical trial and a prospective observational study. I have several comments regarding their methods that I believe are important to consider when interpreting their results.

First, the authors derived the probabilities of dyskinesias and fluctuations from a subgroup of subjects enrolled in the 5-year PKD5009 randomized trial of cabergoline vs levodopa as initial treatment for Parkinson's disease.[2] In this trial, levodopa could be added to cabergoline or additional levodopa given to the levodopa arm after the initial period of titration. However, Smala and coworkers chose to restrict the cohort from which they derived probabilities of motor complications to subjects who never required additional levodopa over the 5 years of the trial. This strategy represents 37% of the original cohort randomized to cabergoline and 54% of those randomized to levodopa. The frequency with which an individual may remain on cabergoline monotherapy over 10 years with satisfactory control of parkinsonism has not been defined but seems likely to be quite small, as it is a minority even over 5 years. Furthermore, these individuals are likely to be systematically different from those who did require the addition of levodopa and cannot be identified before initiating treatment, calling into question the usefulness of this subgroup analysis.

Second, I question whether or not cabergoline and levodopa are being fairly compared by this choice of subgroups. As described above, the subjects of this cost-effectiveness analysis are already a smaller proportion of the cabergoline-treated group than of the levodopa-treated group. Furthermore, the incidence of motor complications in the cabergoline monotherapy subgroup is only 23% (5 of 22) of the entire cabergoline-randomized group from the clinical trial. In comparison, the incidence of motor complications in the levodopa subgroup, was 44% (15 of 34) of the entire group randomized to levodopa. This difference in proportions suggests that the subgroup analysis may not fairly portray the propensity of the two treatments to cause motor complications. It is not clear why data from the entire cohort enrolled in the clinical trial was not used, which would have resulted in a comparison of treatment strategies more relevant to clinical practice.

Third, Smala and colleagues have modelled a 10-year period, which necessitated assumptions regarding the rates at which subjects would develop motor complications over the later years. They assume that the incidence of motor complications is the same over years 5 to 10 as over the first 5 years. This seems implausible, and although we admittedly do not have good estimates of these long-term frequencies, sensitivity analyses modeling increasing rates of motor complications could have defined how their results would change through a plausible range of rates.

I commend Smala and coworkers in gathering data from diverse sources to address a complex and important question. However, their results should be interpreted with careful attention to the fact that they apply to a subgroup of patients able to maintain cabergoline monotherapy for at least 5 years and hypothetically out to 10 years. In addition, although the authors have attempted to create a comparable levodopa subgroup, the two groups are not equally representative of the clinical trial treatment arms from which they were derived. This difference has the potential to have significantly biased their analysis in favor of cabergoline.

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