

Katarzyna Smilowska PhD<sup>1,2</sup>

Tomasz Pietrzykowski PhD<sup>3</sup>

Alexander Calvano<sup>4,5</sup>

K Ray Chaudhuri DSc<sup>4,5</sup>

Daniel J van Wamelen PhD<sup>2,4,5</sup>

<sup>1</sup> Silesian Center of Neurology, Katowice, Poland

<sup>2</sup> Radboud University Medical Center; Donders Institute for Brain, Cognition and Behaviour; Department of Neurology; Centre of Expertise for Parkinson & Movement Disorders; Nijmegen, the Netherlands

<sup>3</sup> Faculty of Law and Administration, University of Silesia, Katowice, Poland

<sup>4</sup> Institute of Psychiatry, Psychology & Neuroscience; Department of Basic & Clinical Neuroscience, Division of Neuroscience; King's College London; London, United Kingdom

<sup>5</sup> Parkinson Foundation Centre of Excellence at King's College Hospital NHS Foundation Trust; and Kings College London, United Kingdom

# Incremental cost-effectiveness ratios for Parkinson's disease patients comparing advanced therapies to best medical treatment

## Introduction

The advanced stage of Parkinson's disease (PD) manifests with progressively increasing disabilities. These usually present as fluctuations between akinetic periods (off phenomenon) and mobile periods (on phenomenon) with or without dyskinesia. At this stage of the disease, treatment aims should shift from oral medication to more continuous dopaminergic stimulation in the form of device-aided therapies, not in the least as these therapies also have a positive effect on many non-motor symptoms, and thus improve quality of life for PD patients. Currently available device-aided therapies are Deep brain stimulation (DBS), intrajejunal Levodopa-carbidopa infusion (IJLI) and continuous subcutaneous apomorphine infusion (CSAI). Here, we aimed to perform a systematic review of the available literature on economic analyses of device-aided therapies in patients with PD in order to assess the cost-effectiveness of these therapies.

## Methods

References used in the current review were identified by performing a systematic search in the PubMed and Web of Science databases in accordance with the PRISMA statement [1]. The search query was based on the PICO strategy and included Parkinson's disease representing 1) Population: Parkinson's disease 2) Intervention: CSAI, IJLI, or DBS; 3) Context/setting: all countries; and 4) Outcomes: cost-effectiveness (of device-aided therapies). As universal guidelines on what is considered cost-effective are lacking, and marked differences in reimbursement policies exist between countries, we decide to use the gross domestic threshold (GDP) as a threshold for cost-ineffectiveness [2]. The GDP of each country in the year in which a study was performed was used to determine whether the device-aided therapy studied was cost-effective (defined by a cost beneath the GDP of the respective country). Information on GDP was downloaded from the Organisation for Economic Co-operation and Development (www.oecd.org)

## Results

| DBS Study                        | Country        | Cost of Intervention | QALYs intervention | Comparator | Cost of Comparator   | QALYs Comparator | Temporal Horizon | Discount Rate | ICER                | Difference in QALY | Incremental Cost   | GDP/capita threshold |
|----------------------------------|----------------|----------------------|--------------------|------------|----------------------|------------------|------------------|---------------|---------------------|--------------------|--------------------|----------------------|
| Tomaszewski and Holloway, [2001] | United States  | \$452,000 (€502,222) | 7.8                | BMT        | \$417,000 (€463,333) | 7.08             | Lifetime         | 3%            | \$49,194 (€54,660)  | 0.72               | \$35,000 (€38,889) | \$37,100             |
| Gerzeli et al. [2002]            | Italy          | €20,033              | NA                 | BMT        | €8,976               | NA               | 1y               | NA            | NS                  | NA                 | €11,057            | \$28,716             |
| Meissner et al. [2005]           | Germany        | €28,305              | NA                 | BMT        | €15,991              | NA               | 2 y              | 5%            | NS                  | NA                 | €12,314            | \$32,237             |
| Valdeoriola et al. [2007]        | Spain          | €27,614              | 0.7611             | BMT        | €20,013              | 0.5401           | 1 y              | NA            | €34,389             | 0.221              | €7,601             | \$32,429             |
| Dams et al. [2013]               | Germany        | €133,174             | 11.62              | BMT        | €126,180             | 10.58            | Lifetime         | 3%            | €6,677              | 1.05               | €6,994             | \$44,994             |
| Valdeoriola et al. [2013]        | Spain          | €103,730             | NA                 | IJLI       | €247,918             | NA               | 5 y              | NS            | NS                  | NA                 | €-144,188          | N/A                  |
|                                  |                |                      |                    | CSAI       | €160,150             | NA               |                  |               | NS                  | NA                 | €-56,420           | N/A                  |
| Eggington et al. [2014]          | United Kingdom | £68,970 (€101,426)   | 2.21               | BMT        | £48,243 (€70,946)    | 1.21             | 5 y              | 3.5%          | £20,678 (€30,409)   | 1.002              | £20,727 (€30,481)  | \$41,269             |
| Zhu et al. [2014]                | China          | \$398,110 (€299,331) | 0.855              | BMT        | \$107,258 (€80,645)  | 0.5              | 2 y              | 3%            | \$24,868 (€18,698)  | 0.355              | \$1,347 (€1,013)   | \$13,459             |
| Walter & Odin et al. [2015]      | UK             | £87,730 (€120,178)   | 2.75               | BMT        | £76,793 (€105,196)   | 2.62             | 3 years          | 3.5%          | NS                  | 0.13               | £10,937 (€14,982)  | \$42,522             |
|                                  | Germany        | €105,737             | 2.85               | BMT        | €90,012              | 2.73             | 3 years          | 3%            | NS                  | 0.12               | €15,725            | \$47,684             |
| Pietzsch et al. [2016]           | USA            | \$130,510 (€117,577) | 3.19               | BMT        | \$91,026 (€82,005)   | 1.50             | 10y              | 3%            | \$23,404 (€21,085)  | 1.69               | \$19,571 (€17,632) | \$57,884             |
| Fundament et al. [2016]          | UK             | £73,077 (€89,118)    | 6.69               | BMT        | £46,278 (€56,437)    | 5.35             | 15y              | 3.5%          | £19,887 (€24,252)   | 1.34               | £26,799 (€32,682)  | \$44,138             |
| Kawamoto et al. [2016]           | Japan          | \$144,600 (€130,270) | NS                 | BMT        | NS                   | NS               | NS               | NS            | NS                  | 6.7                | \$25,600 (€23,063) | \$39,990             |
| Dams et al. [2016]               | Germany        | €151,800             | 13.84              | BMT        | €115,400             | 12.25            | Lifetime         | 3%            | €22,710             | 1.59               | €36,400            | \$50,564             |
| Vivancos-Matellano et al. [2016] | Spain          | €89,477              | 2.80               | IJLI       | €234,643             | 3.12             | 5 years          | 3.5%          | NS                  | -0.32              | €-145,166          | N/A                  |
|                                  |                |                      |                    | CSAI       | €110,348             | 2.89             |                  |               | €245,541            | -0.09              | €-20,817           | N/A                  |
| McIntosh et al. [2016]           | UK             | £19,069 (€23,255)    | 0.0286             | BMT        | £9,813 (€11,967)     | 0.0088           | 1 year           | 3.5%          | £468,528 (€571,376) | 0.02               | £9,256 (€11,288)   | \$44,138             |
|                                  |                | £113,075 (€137,896)  | 4.66               | BMT        | £71,146 (€86,763)    | 4.06             | 10 years         | 3.5%          | £70,537 (€86,021)   | 0.60               | £41,929 (€51,133)  | \$44,138             |

| CSAI Study                       | Country  | Cost of Intervention | QALYs intervention | Comparator | Cost of Comparator | QALYs Comparator | Temporal Horizon | Discount Rate | Difference in QALY | Incremental Cost | ICER per QALY                       | GDP/capita threshold |
|----------------------------------|----------|----------------------|--------------------|------------|--------------------|------------------|------------------|---------------|--------------------|------------------|-------------------------------------|----------------------|
| Kristiansen et al. [2009]        | Sweden   | SEK 562,000          | 1.48               | BMT        | SEK 172,000        | 1.42             | 2 years          | 3%            | 0.06               | SEK 390,000      | SEK 6,100,000 (€665,213)            | \$40,187             |
| Lowin et al. [2011]              | UK       | £201,192             | 1.88               | BMT        | £161,548           | 0.78             | Lifetime         | NS            | 1.10               | £39,644          | £36,024 (€41,407)                   | \$37,146             |
| Kamshveva et al. [2013]          | Bulgaria | BGN 5,655.91         | 57.42 (UPDRS)      | BMT        | BGN 143.49         | 22.67 (UPDRS)    | NS               | NS            | 34.75 (UPDRS)      | BGN 1903.56      | BGN 158.63 (€81.45) per point UPDRS | \$16,582             |
| Lundqvist et al. [2014]          | Norway   | NOK 890,920          | 0.68               | BMT        | NOK 419,160        | 0.63             | 1 year           | NS            | 0.05               | NOK 471,760      | NOK 9,200,000 (€1,180,000)          | \$65,986             |
| Walter & Odin [2015]             | UK       | £130,011             | 3.06               | BMT        | £76,793            | 2.62             | 3 years          | 3.5%          | 0.44               | £53,218          | £120,950 (€165,685)                 | \$42,522             |
|                                  | Germany  | €175,004             | 3.18               | BMT        | €90,012            | 2.73             | 3 years          | 3%            | 0.45               | €84,989          | €188,864                            | \$47,684             |
| Vivancos-Matellano et al. [2016] | Spain    | €234,643             | 3.12               | CSAI       | €110,348           | 2.89             | 5 years          | 3.5%          | 0.23               | €124,295         | €75,206                             | \$37,310             |
|                                  |          |                      |                    | DBS        | €89,477            | 2.80             |                  |               | 0.32               | €146,166         |                                     | \$37,310             |
| Lowin et al. [2017]              | UK       | £537,687             | 4.37               | BMT        | £514,037           | 3.49             | Lifetime         | NS            | 0.88               | £23,650          | £26,944                             | \$45,998             |
| Kalabina et al. [2019]           | UK       | £433,154             | 4.56               | BMT        | £367,653           | 3.30             | 20 years         | NS            | 1.26               | £65,501          | £52,110 (€59,216)                   | \$48,092             |

| IJLI Study                       | Country | Cost of Intervention | QALYs intervention | Comparator | Cost of Comparator | QALYs Comparator | Temporal Horizon | Discount Rate | Difference in QALY | Incremental Cost | ICER per QALY   | GDP/capita threshold |
|----------------------------------|---------|----------------------|--------------------|------------|--------------------|------------------|------------------|---------------|--------------------|------------------|-----------------|----------------------|
| Walter & Odin [2015]             | UK      | £78,251              | 2.85               | BMT        | £76,793            | 2.62             | 3 years          | 3.5%          | 0.23               | £1,458           | £6,440 (€8,822) | \$42,522             |
|                                  | Germany | €104,500             | 2.92               | BMT        | €90,012            | 2.73             | 3 years          | 3%            | 0.19               | €14,488          | €74,696         | \$47,684             |
| Vivancos-Matellano et al. [2016] | Spain   | €110,348             | 2.89               | IJLI       | €234,643           | 3.12             | 5 years          | 3.5%          | -0.23              | €-124,295        | €38,249         | \$37,310             |
|                                  |         |                      |                    | DBS        | €89,477            | 2.80             |                  |               | 0.09               | €20,871          |                 | \$37,310             |

## Discussion & Conclusion

As evidenced in the tables nearly all studies with a temporal horizon of five years or over show that the ICER for the three device-aided was less than the GDP for the countries where the respective studies were conducted. As such, all three device-aided therapies for PD can be considered cost-effective. The cost-effectiveness for DBS appears to be better than for the infusion therapies, but differences in PD populations and more stringent selection criteria for DBS should be acknowledged and studies directly comparing these three device-aided therapies are limited.

Whether or not therapies are deemed cost-effective often depends on health authority regulations in individual countries. In the UK, where many of the included studies in this review were performed, the National institute for Health and Care excellence will often only appraise new medication if the ICER is less than £20,000-£30,000/QALY. However, this situation is not uniform and the 'willingness to pay' per QALY differs vastly across countries [3]. Although fixed criteria to assess whether an intervention is cost-effective are lacking and differ from country to country, some studies, e.g. by Laupacis et al., proposed that treatment ought to be considered cost-effective if the costs were below €50,000/QALY [49]. However, the benchmark recommended by WHO and deployed in this review, uses rather GDP-ICER comparison as the basic measure of therapy's cost-effectiveness.[2].

## References

- Liberati A et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62: e1-34.
- Kamshveva MS et al. Intestinal gel Levodopa+ Carbidopa in Parkinson's patients with frequent and prolonged akinesia-an economic evaluation. Int J Pharm Sci Rev Res 2013; 22: 244-246.
- Cameron D et al. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. Global health action 2018; 11: 1447828.

## Acknowledgements

KS was supported by the CoCoCare programme of the European Academy of Neurology