Treatment of Advanced Parkinson's Disease in the United States: A Cost-Utility Model

Huybert Groenendaal[1], Marcy Tarrants[2] and Christophe Armand[3]

[1]Vose Consulting, *Boulder, CO*   [2]Teva Neuroscience, *Kansas City, MO*   [3]H. Lundbeck A/S, *Paris, France*

1 Background

Parkinson's disease (PD) is a neurologic disorder affecting approximately 1% of the US population over 65 years of age and its advanced stages result in debilitating symptoms such as muscle rigidity, tremors at rest, bradykinesia, and postural instability (Tanner et al., 1996). Such motor-fluctuations, also called "off-time", have considerable impact on the quality of life of patients and places a heavy economic burden on patients, their family, and society.

A number of treatment options are available for patients with advanced PD who experience motor fluctuations, including:

- Rasagiline has been approved as a monotherapy in early PD or as an adjunct therapy with simultaneous levodopa (LD) in patients with advanced PD who experience motor fluctuations.
- Entacapone (COMT) improves the bioavailability and prolongs the half-life of levodopa. Because entacapone is recommended by most experts as the standard adjunct treatment for patients taking levodopa who experience motor fluctuations and because of its widespread use, entacapone is a relevant comparator for rasagiline.
- Levodopa/carbidopa/entacopone (LCE) is a combination of carbidopa, LD and COMT and is used as a second comparator for rasagiline.

The cost-effectiveness of rasagiline has so far only been estimated for treatment of patients with advanced PD in Finland (Hudry et al., 2006).

2 Study Objectives

The purpose of this study is to assess the costs and effectiveness of rasagiline or COMT as adjunctive therapies to LD (+LD) or LCE versus standard LD monotherapy in patients with advanced PD and motor fluctuations in the US.

3 Methods

This cost-effectiveness study was performed from a societal perspective and from the perspective of a third-party payor. A Markov model was developed and used to estimate the expected costs and benefits (including second-order uncertainty) of an advanced PD patient with motor fluctuations. The Markov model considered three separate health statuses as shown in Figure 1. Six time-steps (i.e. cycles), each of four months, were simulated, for a total horizon of two years.
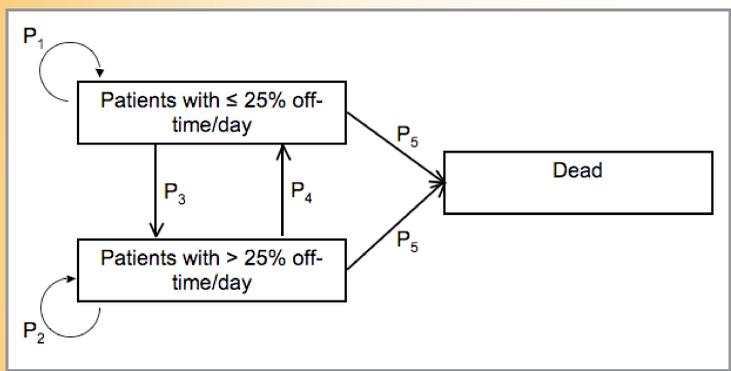
Figure 1. *Graphic overview of the Markov model. P1 is probability of staying in ≤25% off-time/day health status, P2 is probability of staying in >25% off-time/day health status, P3 is probability of going from ≤25% off-time/day health status to >25% off-time/day health status, P4 is probability of going from >25% off-time/day health status to ≤25% off-time/day health status, and P5 is probability of dying*

The transition probabilities between the ≤25% off-time/day and >25% off-time/day (p1, p2, p3 and p4) were estimated based on the LARGO study (Rascol et al., 2005) and study extension. To estimate the probability of mortality (p5), the Declining Exponential Approximation of Life Expectancy (DEALE) was used in conjunction with results from Herlofsen et al. (2006).

The expected costs and utilities over a two year period were based on the expected transitions of a patient between the different health statuses. The incremental cost-effectiveness ratio (ICER) was calculated for each of the comparators versus standard care (levodopa monotherapy). The following three comparators were taken into account:

1. Rasagiline as adjunctive therapy to LD;
2. Entacapone (COMT) as adjunctive therapy to LD
3. Levodopa/carbidopa/entacopone (LCE)

The nondrug direct medical costs were derived from Orsini et al. (2004). Outpatient pharmaceutical costs were not included in the total per patient costs.

Type of Service	n	Sample Mean	Sample SD	SEM
Inpatient Admissions	5440	$ 9,362	$ 18,816	$ 255
Long-Term Care	1653	$ 2,282	$ 6,829	$ 168
Emergency Department Visits	3553	$ 60	$ 273	$ 5
Outpatient Visits	9718	$ 581	$ 489	$ 5
Outpatient Therapy (OT, PT, Speech)	2479	$ 142	$ 578	$ 12
Outpatient DME (wheelchair, walker, etc.)	5347	$ 365	$ 2,022	$ 28

Table 1. *Annual nondrug direct medical costs by service type (from Orsini et al., 2004)*

The indirect medical costs were assumed to be equal to nondrug direct medical costs. In addition, a 2:1 cost ratio of nondrug direct medical costs and indirect costs for patients with >25% off-time/day was assumed: ≤25% off-time/day (Dodel et al., 2001).

The drug related costs were based on the defined daily doses (DDD) as established by the World Health Organization Collaborating Centre for Drug Statistics Methodology (2009).

Drug	Retail prices in US$ per DDD
Levodopa	4.09
Entacapone	12.15
Rasagiline	8.37
Levodopa/carbidopa/entacopone (LCE)	11.95

Table 2. *Drug prices used within the model*

Within the Markov model, a number of probability distributions were used to reflect the second-order uncertainty (in isolation) regarding the different input parameters used in the model and 100,000 Monte Carlo simulation trials of the Markov model were run to obtain the final results.

4 Study Results

The results of the costs and effectiveness study show that over 2 years, all three therapy arms show greater effectiveness (QALY's as well as Months ≤25% off-time) than LD alone. Rasagiline +LD show a slightly higher expected effectiveness than the other two treatment arms. With regards to the total direct medical costs and total costs, COMT +LD show the highest costs followed by LD monotherapy, rasagiline +LD and LCE.

The results of the incremental effectiveness, incremental cost and ICER are show in Table 3.

Table 3. *Mean, SEM and 90% credibility interval of the incremental effectiveness and cost and ICER of standard care versus the three treatment arms over a two year horizon. Confidence represents the confidence that the treatment arm is higher than standard care (LD monotherapy)*

Parameters	Mean	SEM	5%	95%	Confidence*
Incremental effectiveness comparator vs. standard care					
QALY					
Rasagiline + LD	0.123	0.030	0.076	0.175	100.0%
COMT + LD	0.117	0.030	0.071	0.168	100.0%
LCE	0.117	0.030	0.071	0.168	100.0%
Month ≤ 25% off-time					
Rasagiline + LD	5.082	0.732	3.867	6.275	100.0%
COMT + LD	4.851	0.739	3.633	6.063	100.0%
LCE	4.851	0.739	3.633	6.063	100.0%
Incremental costs comparator vs. standard care					
Direct medical costs					
Rasagiline + LD	$ (1,666)	$ 1,045	$ (3,382)	$ 53	5.6%
COMT + LD	$ 1,147	$ 1,055	$ (587)	$ 2,881	86.2%
LCE	$ (1,710)	$ 1,055	$ (3,445)	$ 25	5.2%
Total costs					
Rasagiline + LD	$ (8,843)	$ 2,092	$ (12,287)	$ (5,403)	0.0%
COMT + LD	$ (5,704)	$ 2,111	$ (9,175)	$ (2,237)	0.4%
LCE	$ (8,561)	$ 2,112	$ (12,034)	$ (5,094)	0.0%
ICER comparator vs. standard care					
Direct medical costs, QALY					
Rasagiline + LD	$ (13,143)	$ 8,347	$ (25,859)	$ 570	5.6%
Entacapone (COMT)	$ 12,031	$ 12,897	$ (4,074)	$ 35,487	86.2%
LCE	$ (14,089)	$ 8,802	$ (27,375)	$ 268	5.2%
Direct medical costs, months with ≤ 25%					
Rasagiline + LD	$ (304)	$ 175	$ (542)	$ 14	5.6%
Entacapone (COMT)	$ 278	$ 283	$ (97)	$ 790	86.2%
LCE	$ (326)	$ 184	$ (571)	$ 7	5.2%

Benefits (i.e. incremental effectiveness) over 2 years were 0.12 additional QALY's for rasagiline +LD, COMT +LD and LCE and 5.08 additional months with ≤25% off-time for rasagiline +LD and 4.85 for COMT +LD and LCE versus LD alone.

Rasagiline +LD and LCE resulted in additional direct medical costs of respectively -$13,135 and -$14,104 per additional QALY and -$304 and -$326 per additional months ≤25% off-time/day. The negative ICER's of rasagiline +LD and LCE show lower total direct medical costs of both treatments compared to standard treatment together with higher effectiveness.

COMT +LD resulted in a $12,018 additional direct medical costs per QALY and an additional direct medical costs of $278 per additional month with ≤25% off-time/day. The positive ICER's were a result of the higher costs of COMT +LD compared to LD monotherapy together with the higher effectiveness.

Based on the model, there is a 100% confidence that the effectiveness (QALY's and months ≤25% off-time) of all treatment arms is larger than LD monotherapy. The confidence levels for the direct medical costs of standard care being larger than those of rasagiline +LD, COMT +LD and LCE are respectively 5.7%, 13.8% and 5.3%. Finally, the confidence level for the total costs of LD monotherapy being higher than either of the three treatment arms is 99.6% (100% minus 0.4%)

In addition, rasagiline +LD, COMT +LD and LCE are dominant treatments to LD monotherapy (i.e. lower costs with higher effectiveness). The confidence levels are respectively 94.3%, 13.8% and 94.7% confidence (100% minus the confidence levels shown in Table 3).

The four figures below show incremental cost-effectiveness planes from both the payor and society perspectives.
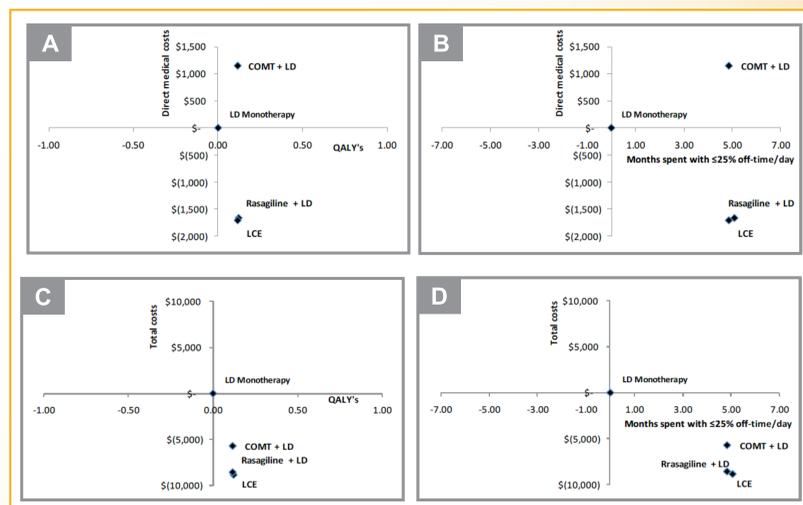
Figure 2. *Incremental cost-effectiveness planes. Payor perspective – expected QALY's (A) and months spent with ≤25% off-time/day (B). Societal perspective – expected QALY's (C) and months spent with ≤25% off-time/day (D). QALY's = quality adjusted life years.*

The COMT +LD treatment, as show in the upper right-hand plane (Figure 2A and 2B), provides a higher effectiveness, but at higher costs to the payor. All other treatments are positioned in the lower right-hand plane, which means they are dominant to LD monotherapy (i.e. lower costs, higher effectiveness).

5 Conclusion

The current study provides valuable insight into the cost-effectiveness of four alternative treatments of patients with advanced PD and motor fluctuations in the US. The results presented in this paper support the use of rasagiline adjunctively to LD and LCE as cost-effective treatments of patients with advanced PD and motor fluctuations in the US. Treatment with rasagiline +LD and LCE provided costs savings from a societal as well as from a payor perspective, as compared to the standard LD monotherapy, and in addition showed a higher effectiveness (increased QALY's and increased number of months ≤25% off-time/day). Very similar benefits were found for rasagiline +LD as for LCE, which is driven by the LARGO clinical trial data showing similar results for rasagiline +LD or COMT +LD and the subsequent assumption of equal transition probabilities for COMT +LD and LCE. Furthermore, the study showed that COMT +LD was a more effective treatment than standard care, but would result in higher expected total costs to society.

In conclusion, with no additional cost over a 2 year period, rasagiline +LD presents a beneficial alternative to COMT +LD, LCE and LD monotherapy in the treatment of advanced PD patients. Results from this cost-utility model and prior adjunctive clinical data (i.e. Rascol et al., 2005) provides ongoing support for rasagiline's adjunctive use in moderate to advanced PD patients with motor fluctuations in the US.

6 References

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