

# Critical appraisal of rotigotine transdermal system in management of Parkinson's disease and restless legs syndrome – patient considerations [Corrigendum]

Kesayan T, Shaw JD, Jones TM, Staffetti JS, Zesiewicz TA. Degenerative Neurological and Neuromuscular Disease 2015;5:63–72.

The authors would like to correct the following errors: on page 64; paragraph 1, “RTG doses for treatment of early-stage PD monotherapy range from 2 mg/24 hours to 6 mg/24 hours, with recommended titration of 2 mg/24 hours weekly.<sup>5</sup> For adjunct therapy in advanced-stage PD, RTG may be started at 4 mg/24 hour period and titrated up weekly by an additional 2 mg/24 hour period, with a maximum recommended dose of 16 mg/24 hours.”<sup>7</sup> should be “RTG doses for treatment of early-stage PD monotherapy range from 2 mg/24 hours to 8 mg/24 hours (2–6 mg/24 hours in the US), with recommended titration of 2 mg/24 hours weekly.<sup>5</sup> For adjunct therapy in advanced-stage PD, RTG may be started at 4 mg/24 hour period and titrated up weekly by an additional

2 mg/24 hour period, with a maximum recommended dose of 16 mg/24 hours (4–8 mg/24 hours in the US).<sup>5</sup>”

On page 64; paragraph 5, “The mean RTG dose was 8 mg/24 hours, while the mean ropinirole dose was 14.1 mg/day.” should have been “The majority of patients (92%) received RTG maintenance dose of 8 mg/24 h, while the median ropinirole dose was 14.1 mg/day.”

On page 64; paragraph 6, “Three hundred and forty-one patients were randomized to receive RTG 8 mg/24 hours, 12 mg/24 hours, or placebo for 28 weeks.” should have been “Three hundred and forty-one patients were randomized to receive RTG up to 8 mg/24 hours, up to 12 mg/24 hours, or placebo for 28 weeks.”

On page 65; Table 1, data in the Doses column and the Notes section have been updated.

**Table 1** Efficacy of RTG in early and advanced PD

|                                     | Dose (mg/24 hour)           | n   | Change from baseline ± SD (P-value) |                     |
|-------------------------------------|-----------------------------|-----|-------------------------------------|---------------------|
|                                     |                             |     | UPDRS II ADL                        | UPDRS III motor     |
| Early PD                            |                             |     |                                     |                     |
| Güldenpfennig et al <sup>120</sup>  | 8 mg/24 hour <sup>a</sup>   | 25  | −2.84±3.45 (0.0004)                 | −4.88±5.56 (0.0002) |
|                                     | <8 mg/24 hour <sup>a</sup>  | 4   | −2.25±2.36 (0.1622)                 | −3.00±3.56 (0.1671) |
|                                     | Plo                         | 0   | –                                   | –                   |
| Jankovic et al <sup>121</sup>       | 5.7 mg/24 hour <sup>b</sup> | 177 | −0.39 ±0.26 (0.002)                 | −3.58±0.54 (0.001)  |
|                                     | Plo                         | 96  | 0.92±0.35 (0.002)                   | 0.38±0.73 (0.001)   |
| Parkinson Study Group <sup>22</sup> | 2 mg/24 hour <sup>a</sup>   | 49  | −0.04 (0.94)                        | −0.90 (0.44)        |
|                                     | 4 mg/24 hour <sup>a</sup>   | 47  | −0.84 (0.11)                        | −1.88 (0.11)        |
|                                     | 6 mg/24 hour <sup>a</sup>   | 48  | −0.92 (0.08)                        | −3.91 (0.001)       |
|                                     | 8 mg/24 hour <sup>a</sup>   | 51  | −1.56 (0.003)                       | −3.82 (0.001)       |
|                                     | Plo                         | 47  | –                                   | –                   |
| Watts et al <sup>123</sup>          | 5.7 mg <sup>b</sup>         | 180 | −0.30±3.54                          | −3.50±7.26          |
|                                     | Plo                         | 96  | –                                   | –                   |
| Giladi et al <sup>2</sup>           | 8 mg <sup>c</sup>           | 215 | −2.1 <sup>d</sup>                   | −5.2 <sup>d</sup>   |
|                                     | Plo                         | 118 | −0.1                                | −2.1                |
| Trenkwalder et al <sup>125</sup>    | 2–16 mg                     | 178 | −2.6±3.6                            | −7.0 (0.002)        |
|                                     | Plo                         | 89  | −1.3±3.4                            | −3.9                |
| Advanced PD                         |                             |     |                                     |                     |
| LeWitt et al <sup>126</sup>         | ≤8 mg/24 h                  | 113 | −3.1 (0.004)                        | −6.8 (0.0185)       |
|                                     | ≤12 mg/24 h                 | 109 | −3.2 (0.0023)                       | −8.7 (0.0006)       |
|                                     | Plo                         | 119 | −0.5                                | −3.4                |

(Continued)

**Table 1** (Continued)

|                           | Dose (mg/24 hour) | n   | Change from baseline $\pm$ SD (P-value) |                          |
|---------------------------|-------------------|-----|---|--------------------------|
|                           |                   |     | UPDRS II ADL                            | UPDRS III motor          |
| Poewe et al <sup>27</sup> | 4–16 mg/24 hour   | 201 | –4.2 $\pm$ 4.5 (<0.0001)                | –8.7 $\pm$ 8.0 (<0.0001) |
|                           | Plo               | 100 | –2.0 $\pm$ 4.3 (<0.0001)                | –4.3 $\pm$ 9.3 (<0.0001) |

**Notes:** <sup>a</sup>RTG content per system (mg) originally reported; RTG nominal doses (mg/24 h) were calculated using a ratio of 2.25 (as per US prescribing information<sup>3</sup>), ie, 4.5 mg is equivalent to 2 mg/24 h, 9 mg to 4 mg/24 h, 13.5 mg to 6 mg/24 h, and 18 mg to 8 mg/24 h; <sup>b</sup>The mean (SD) dose was 5.7 (0.84) mg/24 h; 6 mg dose for majority of participants; <sup>c</sup>Ninety-two percent of those in the RTG group were treated with this dose in the maintenance phase and 8% had lower doses; there was no SD reported for UPDRS II or III separately; however, the combined UPDRS part III + part II scores were significantly more improved compared to placebo at the end of the maintenance phase ( $P<0.0001$ ); <sup>d</sup>there was no SD reported for UPDRS II or III separately, however the combined UPDRS part III + part II scores were significantly more improved compared to placebo at the end of the maintenance phase ( $P<0.0001$ ).

**Abbreviations:** RTG, rotigotine; PD, Parkinson's disease; UPDRS II, Unified Parkinson's Disease Rating Scale part II (activities of daily living); UPDRS III, Unified Parkinson's Disease Rating Scale part III (motor examination); Plo, placebo.

**Table 3** Efficacy of RTG in RLS – change from baseline  $\pm$  SD (P-value)

| Study, dose (mg/24 hour)       | n   | IRLS total score $\pm$ SD (P-value) | CGI-I score $\pm$ SD (P-value) | PSQI total score $\pm$ SD (P-value) |
|--------------------------------|-----|-------------------------------------|--------------------------------|-------------------------------------|
| Inoue et al <sup>40</sup>      |     |                                     |                                |                                     |
| 2 mg                           | 95  | –14.3 $\pm$ 8.9 (0.030)             | –                              | –3.1 $\pm$ 3.2 (0.188)              |
| 3 mg                           | 94  | –14.6 $\pm$ 9.0 (0.016)             | –                              | –3.2 $\pm$ 3.3 (0.112)              |
| Plo                            | 95  | –11.6 $\pm$ 8.2                     | –                              | –2.5 $\pm$ 2.4                      |
| Oertel et al <sup>24</sup>     |     |                                     |                                |                                     |
| 2 mg <sup>a</sup>              | 41  | –16.5 $\pm$ 9.3                     | –2.7 $\pm$ 1.4                 | –                                   |
| Plo                            | 20  | –9.9 $\pm$ 9.9                      | –1.7 $\pm$ 1.5                 | –                                   |
| Hening et al <sup>10</sup>     |     |                                     |                                |                                     |
| 0.5 mg                         | 98  | –10.9 $\pm$ 8.9 (0.0682)            | 4.7 $\pm$ 0.8 (0.0603)         | –                                   |
| 1 mg                           | 99  | –11.1 $\pm$ 9.3 (0.0535)            | 4.6 $\pm$ 0.7 (0.0857)         | –                                   |
| 2 mg                           | 95  | –13.4 $\pm$ 9.2 (0.0002)            | 4.7 $\pm$ 0.8 (0.0007)         | –                                   |
| 3 mg                           | 103 | –14.3 $\pm$ 9.4 (<0.0001)           | 4.7 $\pm$ 0.8 (<0.0001)        | –                                   |
| Plo                            | 99  | –9.0 $\pm$ 7.7                      | 4.7 $\pm$ 0.6                  | –                                   |
| Trenkwalder et al <sup>8</sup> |     |                                     |                                |                                     |
| 1 mg                           | 148 | –14.0 $\pm$ 0.8 (<0.0001)           | –2.13 $\pm$ 0.12 (<0.0001)     | –                                   |
| 2 mg                           | 96  | –16.4 $\pm$ 1.0 (<0.0001)           | –2.41 $\pm$ 0.14 (<0.0001)     | –                                   |
| 3 mg                           | 92  | –16.8 $\pm$ 1.1 (<0.0001)           | –2.55 $\pm$ 0.17 (<0.0001)     | –                                   |
| Plo                            | 111 | –8.7 $\pm$ 0.9                      | –1.37 $\pm$ 0.15               | –                                   |
| Oertel et al <sup>9</sup>      |     |                                     |                                |                                     |
| 0.5 mg                         | 50  | –10.5 $\pm$ 9.2 (0.2338)            | –1.6 $\pm$ 1.4                 | –                                   |
| 1 mg                           | 64  | –15.3 $\pm$ 10.0 (0.0004)           | –2.2 $\pm$ 1.5 (<0.05)         | –                                   |
| 2 mg                           | 49  | –15.7 $\pm$ 9.5 (0.0003)            | –2.4 $\pm$ 1.3 (<0.05)         | –                                   |
| 3 mg                           | 64  | –17.3 $\pm$ 10.5 (<0.0001)          | –2.7 $\pm$ 1.6 (<0.05)         | –                                   |
| 4 mg                           | 53  | –14.9 $\pm$ 10.3 (0.0013)           | –2.3 $\pm$ 1.5 (<0.05)         | –                                   |
| Plo                            | 53  | –9.3 $\pm$ 9.6                      | –1.5 $\pm$ 1.4                 | –                                   |
| Stiasny-Kolster <sup>41</sup>  |     |                                     |                                |                                     |
| 0.5 mg/24 hour <sup>b</sup>    | 19  | –10.5 $\pm$ 2.0                     | –                              | –                                   |
| 1 mg/24 hour <sup>b</sup>      | 13  | –12.3 $\pm$ 2.3                     | –                              | –                                   |
| 2 mg/24 hour <sup>b</sup>      | 17  | –15.7 $\pm$ 1.9                     | –                              | –                                   |
| Plo                            | 14  | –8.0 $\pm$ 2.2                      | –                              | –                                   |

**Notes:** <sup>a</sup>A mean dose of RTG in the treatment group was reported as 2.1 mg/24 hours; <sup>b</sup>RTG content per system (mg) originally reported; RTG nominal doses (mg/24 h) were calculated using a ratio of 2.25 (as per US prescribing information<sup>3</sup>), ie, 1.125 mg is equivalent to 0.5 mg/24 h, 2.25 mg to 1 mg/24 h, and 4.5 mg to 2 mg/24 h.

**Abbreviations:** RTG, rotigotine; RLS, restless legs syndrome; SD, standard deviation; IRLS, International Restless Legs Syndrome Study Group severity rating scale; CGI-I, Clinical Global Impressions item-I; PSQI, Pittsburgh Sleep Quality Index; Plo, placebo.

On page 66; paragraph 2, “In an open-label study, advanced-PD patients were treated with levodopa, pramipexole (<1.5 mg/day), or ropinirole (<6.0 mg/day), and RTG (<8 mg/24 hours) for an 8-week treatment period.”<sup>73</sup> should have been “In an open-label study, advanced-PD patients were treated with levodopa, pramipexole ( $\leq$ 1.5 mg/day), or

ropinirole ( $\leq$ 6.0 mg/day), and RTG ( $\leq$ 8 mg/24 hours) for an 8-week treatment period.”<sup>73</sup>

On page 68; Table 3, data in the Study, doses column for the Stiasny-Kolster study and the Notes section have been updated.

On page 69; Table 4, the data for the Stiasny–Kolster study and the Notes section have been updated.

**Table 4** Side effects present in participants (%) during randomized, double-blinded, placebo-controlled trials

| Side effect               | Dose (mg/24 hour) | Inoue et al <sup>40</sup> |     | Hening et al <sup>10</sup> |      | Trenkwalder et al <sup>8</sup> |     | Oertel et al <sup>9</sup> |     | Oertel et al <sup>24,a</sup> |      | Stiasny–Kolster <sup>41,b</sup> |      |
|---------------------------|-------------------|---------------------------|-----|----------------------------|------|--------------------------------|-----|---------------------------|-----|------------------------------|------|---------------------------------|------|
|                           |                   | RTG                       | Plo | RTG                        | Plo  | RTG                            | Plo | RTG                       | Plo | RTG                          | Plo  | RTG                             | Plo  |
| Application site reaction | 0.5 mg            | –                         | 7.4 | 22.2                       | 5.0  | –                              | –   | 9.8                       | 1.8 | –                            | 4.8  | 17.6                            | 28.6 |
|                           | 1 mg              | –                         | –   | 17                         | –    | 35.0                           | 2.0 | 15.6                      | –   | –                            | –    | 38.5                            | –    |
|                           | 2 mg              | 42.1                      | –   | 34.3                       | –    | 41.0                           | –   | 16.3                      | –   | 17.4                         | –    | 26.3                            | –    |
|                           | 3 mg              | 50.0                      | –   | 34                         | –    | 52.0                           | –   | 20                        | –   | –                            | –    | –                               | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | 25                        | –   | –                            | –    | –                               | –    |
| Headache                  | 0.5 mg            | –                         | 0   | 14.1                       | 8.0  | –                              | –   | 11.8                      | 7.3 | –                            | 14.3 | 11.8                            | 7.1  |
|                           | 1 mg              | –                         | –   | 12                         | –    | 10.0                           | 7.0 | 7.8                       | –   | –                            | –    | 38.5                            | –    |
|                           | 2 mg              | 5.3                       | –   | 10.1                       | –    | 13.0                           | –   | 2                         | –   | 17.4                         | –    | 21.1                            | –    |
|                           | 3 mg              | 2.1                       | –   | 10.4                       | –    | 16.0                           | –   | 4.6                       | –   | –                            | –    | –                               | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | 12.5                      | –   | –                            | –    | –                               | –    |
| Nausea                    | 0.5 mg            | –                         | 9.5 | 13.1                       | 10.0 | –                              | –   | 5.9                       | 9.1 | –                            | 4.8  | 0.0                             | 14.3 |
|                           | 1 mg              | –                         | –   | 20                         | –    | 9.0                            | –   | 9.4                       | –   | –                            | –    | 7.7                             | –    |
|                           | 2 mg              | 33.7                      | –   | 18.2                       | –    | 21.0                           | –   | 6.1                       | –   | 21.7                         | –    | 5.3                             | –    |
|                           | 3 mg              | 43.6                      | –   | 20.8                       | –    | 18.0                           | –   | 24.6                      | –   | –                            | –    | –                               | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | 23.2                      | –   | –                            | –    | –                               | –    |
| Fatigue                   | 0.5 mg            | –                         | –   | 10.1                       | 4.0  | –                              | –   | 3.9                       | 9.1 | –                            | 9.5  | 0.0                             | 0.0  |
|                           | 1 mg              | –                         | –   | 3                          | –    | 7.0                            | 9.0 | 4.7                       | –   | –                            | –    | 0.0                             | –    |
|                           | 2 mg              | –                         | –   | 7.1                        | –    | 15.0                           | –   | 6.1                       | –   | 8.7                          | –    | 10.5                            | –    |
|                           | 3 mg              | –                         | –   | 6.6                        | –    | 11.0                           | –   | 10.8                      | –   | –                            | –    | –                               | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | 7.1                       | –   | –                            | –    | –                               | –    |
| Pruritus                  | 0.5 mg            | –                         | –   | 9.1                        | 2.0  | –                              | –   | 5.9                       | 1.8 | –                            | –    | 5.9                             | 7.1  |
|                           | 1 mg              | –                         | –   | 2                          | –    | –                              | –   | 3.1                       | –   | –                            | –    | 15.4                            | –    |
|                           | 2 mg              | –                         | –   | 3                          | –    | –                              | –   | 0                         | –   | –                            | –    | 0.0                             | –    |
|                           | 3 mg              | –                         | –   | 7.5                        | –    | –                              | –   | 10.8                      | –   | –                            | –    | –                               | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | 3.6                       | –   | –                            | –    | –                               | –    |
| Hyperhidrosis             | 0.5 mg            | –                         | –   | –                          | –    | –                              | –   | –                         | –   | –                            | –    | –                               | 0.0  |
|                           | 1 mg              | –                         | –   | –                          | –    | 5.0                            | 3.0 | –                         | –   | –                            | –    | 0.0                             | –    |
|                           | 2 mg              | –                         | –   | –                          | –    | 6.0                            | –   | –                         | –   | –                            | –    | 0.0                             | –    |
|                           | 3 mg              | –                         | –   | –                          | –    | 4.0                            | –   | –                         | –   | –                            | –    | 10.5                            | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | –                         | –   | –                            | –    | –                               | –    |
| Somnolence                | 0.5 mg            | –                         | 2.1 | 8.1                        | 6.0  | –                              | –   | –                         | –   | –                            | 9.5  | –                               | –    |
|                           | 1 mg              | –                         | –   | 10.0                       | –    | –                              | –   | –                         | –   | –                            | –    | –                               | –    |
|                           | 2 mg              | 10.5                      | –   | 13.1                       | –    | –                              | –   | –                         | –   | 10.9                         | –    | –                               | –    |
|                           | 3 mg              | –                         | –   | 15.1                       | –    | –                              | –   | –                         | –   | –                            | –    | –                               | –    |
|                           | 4 mg              | –                         | –   | –                          | –    | –                              | –   | –                         | –   | –                            | –    | –                               | –    |

**Notes:** <sup>a</sup>The study did not report the association of adverse events (AE) in relation to the dose of RTG. A mean dose of RTG in the treatment group was reported as 2.1 mg/24 hours; <sup>b</sup>RTG content per system (mg) originally reported; RTG nominal doses (mg/24 h) were calculated using a ratio of 2.25 (as per US prescribing information<sup>5</sup>), ie, 1.125 mg is equivalent to 0.5 mg/24 h, 2.25 mg to 1 mg/24 h, and 4.5 mg to 2 mg/24 h.

**Abbreviations:** RTG, rotigotine; Plo, placebo.

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