Ramelteon in the treatment of chronic insomnia: systematic review and meta-analysis

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Introduction

It has been reported that nearly one-third of the adult population in the United States suffers from sleep problems (1). Reported rates of insomnia in other countries include 21% in Japan (2), 19% in France (3) and 18% in Canada (4). It is more prevalent in the older population, which can be attributed to the progressive inactivity, dissatisfaction with social life and presence of illness (5). Except for sleep disturbance, the daytime symptoms of insomnia mainly include fatigue, increased irritability, reduction in motivation, energy or initiative, impairment of social or occupational functioning and reduced quality of life (6). In 1995, the direct costs of insomnia in the United States totalled $13.96 billion (7). Considering its high prevalence and costs, insomnia is therefore a considerable public health challenge.

As a melatonin receptor agonist, ramelteon was approved in the United States as a treatment for insomnia. As a potential alternative, ramelteon should be further evaluated in different doses and populations. This systematic review with meta-analysis aims to determine the efficacy and safety of ramelteon in the treatment of chronic insomnia. Methods: We systematically searched and identified in Medline, Embase, PsycINFO and Cochrane Library until September 2011. We only included randomised controlled trials focused on ramelteon, vs. placebo, or any other treatment for patients with chronic insomnia. Eight studies were selected to include from 175 identified references. There were significant improvements in all the outcomes (subjective and polysomnographic sleep latency, total sleep time and latency to REM), except for the percentage of REM. By subgroup analysis, subjective sleep latency was reduced only in the patients of 18–64 years old, without in the patients over 65 years old. For the safety, ramelteon was not associated with higher risk ratio of any frequent adverse events comparing with control. Conclusion: The efficacy and safety of ramelteon are promising for the chronic insomnia patients. More researches are required for robust conclusions, particularly well-designed; double-blind randomised controlled trials with higher doses of ramelteon (32 or 64 mg) for the older population comparing with other sedative hypnotics.
receptor complexes located throughout the brain. It has little affinity for other receptors, such as MT3, dopaminergic and GABAergic receptors (16). Actually, ramelteon has no significant abuse potential, motor or cognitive impairment even at up to 20 times the recommended therapeutic dose (17).

In previous clinical trials, ramelteon effectively improved the measures of sleep in adults with primary chronic insomnia with less adverse events (18,19). Some studies supported there were no next-day residual effects of ramelteon on the behavioural and cognitive tasks (20), whereas recent study opposed this view (21). Therefore, as a potentially useful alternative to existing insomnia medications, ramelteon should be further evaluated in different doses and populations. This systematic review with meta-analysis aims to determine the efficacy and safety of ramelteon in the treatment of chronic insomnia.

Methods

Search strategy
We carried out a systematic review and meta-analysis of studies that evaluate the efficacy and safety of ramelteon monotherapy for the treatment of primary chronic insomnia in adults. We searched MEDLINE (1966–Sep 2011), EMBASE (1980–Sep 2011), PsycINFO (1974–Sep 2011), Cochrane Library and CNKI (China National Knowledge Infrastructure/Chinese Academic Journals full text Database, 1980–Sep 2011). The MEDLINE search strategy is provided in Appendix 1. International trial registers were searched via the WHO International Clinical Trials Registry Platform (ICTRP) together with the trial register of the Takeda Pharmaceutical Company who developed and market the drug Ramelteon (TAK-375). Reference lists, of the reports of all included trials together with systematic reviews and meta-analyses were scanned to identify additional trials. Active researchers in the field were contacted and asked if they had knowledge of other relevant published or unpublished trials.

Study selection, data extraction and assessment of quality
We only included randomised controlled trials (RCTs) focused on ramelteon, vs. placebo, or any other treatment for patients who suffer from primary chronic insomnia. Uncontrolled, non-randomised or quasi-randomised trials were excluded. Both parallel group and cross-over design were included. The study that involved in the patients 18 years of age and older, who suffered from primary chronic insomnia according to DSM-IV criteria (22) (recurring for at least 3 months) was included. The study was excluded if it enrolled the patients with a significant medical disorder or used any medications that affect central nervous system. The outcomes mainly focused on the subjective sleep latency, subjective total sleep time, polysomnographic (PSG) latency to persistent sleep, PSG total sleep time, percentage of rapid eye movement (REM) stage in total sleep time, latency to REM, next-day residual effects and all kinds of adverse effect. Two review authors (LJ, WL) independently evaluated titles and abstracts of identified trials to determine eligibility. We obtained the full text of all potentially relevant studies for further consideration. Any disagreement was arbitrated by a third party, if necessary. We used checklists to independently record details including study design, population, intervention and risk of bias (randomisation, blinding, withdrawals and allocation concealment).

Data synthesis
We evaluated the differences of outcomes between ramelteon and placebo. Continuous data were expressed as mean differences (MD) and dichotomised data were expressed as risk ratios (RR). We calculated MD and RR with 95% confidence intervals (CI) (23). If neither clinical nor statistical heterogeneity was found, we pooled results using a fixed-effect model. If significant statistical heterogeneity was found (P < 0.05), random-effect model was considered to do the sensitivity analysis. We used the funnel plot method to assess the potential publication bias (24).

Subgroup analysis
To test the robustness of our findings, we repeated the meta-analysis by dose of ramelteon, as well as the age of participants.

Results

Description of study
Using our search methods, 175 references were identified. After screening of titles and abstracts, full papers of 22 studies were obtained and assessed for eligibility. According to inclusion criteria, there were eight studies (18,25–31) selected to include. All the studies were randomised, double blind and placebo controlled. Five RCTs (18,25,26,30,31) described the methods of randomisation; two RCTs (25,26) reported details of allocation concealment. Details of drop-outs or withdrawals were described in all the studies. Summary details of these trials were given in ‘Characteristics of included studies’ (Table 1). Eleven studies were excluded because of the ineligible participants (21,32–41), one was with ineligible outcome
setting (42), one was not RCT (19) and one was identified as repetition (43). Agreement between the review authors on exclusion was 100%.

**Efficacy**

Four studies (25,26,28,30) were combined to see the effect of ramelteon only vs. placebo on subjective sleep latency, which reduced significantly with statistical heterogeneity (MD $4.22 \text{ min}$, $5.66$ to $2.77 \text{ min}$; $p < 0.00001$; test for heterogeneity $p < 0.001$). By random-effect model analysis, there was also significant reduction in subjective sleep latency (MD $7.08$, $10.71$ to $3.99$, $P < 0.00001$; test for heterogeneity $p < 0.001$). In three studies (27,28,30) with extractable data, the increase in subjective total sleep time with ramelteon compared with placebo was 8.72 min (4.94–12.49 min; $p < 0.00001$; test for heterogeneity $p = 0.11$). In two studies (28,30) that compared ramelteon with placebo, the reduction in PSG latency to persistent sleep was $13.08 \text{ min}$ ($-15.78$ to $-10.39 \text{ min}$, $p < 0.00001$; test for heterogeneity $p = 0.37$). In three studies (27,28,30) with extractable data, the mean PSG total sleep time increased by 8.58 min (5.71–11.45 min, $p < 0.00001$; test for heterogeneity $p = 0.08$). Three studies (27,28,30) that reported the percentage of REM in PSG total sleep time for ramelteon vs. placebo had a magnitude of effect of 0.21 ($-0.07$ to $0.49$; $p = 0.15$, test for heterogeneity $p = 0.44$). Two studies (27,30) comparing ramelteon with placebo found the reduction in latency to REM (mean effect size $6.34$, $9.23$ to $3.44$; $p < 0.0001$; test for heterogeneity $p = 0.99$).

**Safety**

There were still significant more subjective reports of at least one adverse effect (seven studies (18,25,27–31)) after treatment than after placebo (risk ratio $1.11$, $1.03$ to $1.20$, $P < 0.01$; test for heterogeneity $P = 0.96$). We also investigated the most frequent adverse effects reported in the clinical trials of ramelteon, that is, headache, nasopharyngitis and somnolence. However, none of them after ramelteon use was significantly greater than after placebo (headache: risk ratio $1.11$, $0.88$–$1.41$, $p = 0.38$, test for heterogeneity $p = 0.98$; nasopharyngitis: risk ratio $1.00$, $0.71$–$1.41$, $p = 0.99$; test for heterogeneity $p = 0.63$; somnolence: risk ratio $1.24$, $0.93$–$1.65$, $p = 0.15$, test for heterogeneity $p < 0.01$). By random-effect model analysis, there was also no significant difference in somnolence (risk ratio $1.74$, $0.91$ to $3.30$, $P = 0.09$, test for heterogeneity $P < 0.01$).

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**Table 1  Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>No. of randomised participants</th>
<th>Intervention</th>
<th>Risk of bias*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erman et al. (18)</td>
<td>Crossover, washout 5–12 days, multicenter</td>
<td>Age range 18–64 years (mean 37.7)</td>
<td>107</td>
<td>Ramelteon 4, 8, 16, 32 mg and placebo. Five 2-night treatment periods, with a 5–12 days washout period between treatments.</td>
<td>A,A,A,A,A,U</td>
</tr>
<tr>
<td>Roth et al. (29)</td>
<td>Parallel, multicenter</td>
<td>Age range 64–93 years (mean 72.4)</td>
<td>829</td>
<td>Ramelteon 4 or 8 mg, 35 nights vs. placebo</td>
<td>A,U,A,A,A,U</td>
</tr>
<tr>
<td>Roth et al. (30)</td>
<td>Crossover, washout 5–12 days, multicenter</td>
<td>Age range 65–83 years (mean 70.7)</td>
<td>100</td>
<td>Ramelteon 4, 8 mg and placebo. Five 2-night treatment periods, with a 5–12 days washout period between treatments.</td>
<td>A,A,A,A,A,U</td>
</tr>
<tr>
<td>Zammit et al. (28)</td>
<td>Parallel, multicenter</td>
<td>Age range 18–64 years (mean 39.3)</td>
<td>405</td>
<td>Ramelteon 8 or 16 mg, 35 nights vs. placebo</td>
<td>A,U,A,A,A,U</td>
</tr>
<tr>
<td>Mayer et al. (27)</td>
<td>Parallel, multicenter</td>
<td>Age range 18–79 years (mean 46.2)</td>
<td>451</td>
<td>Ramelteon 8 mg, 6 months vs. placebo</td>
<td>A,U,A,A,A,U</td>
</tr>
<tr>
<td>Zammit et al. (31)</td>
<td>Crossover, washout 4–10 days, multicenter</td>
<td>Age ≥ 65 years (mean 46.2)</td>
<td>33</td>
<td>Ramelteon 8 mg, one night vs. placebo</td>
<td>A,A,A,A,A,U</td>
</tr>
<tr>
<td>Uchimoto et al. (25)</td>
<td>Parallel, multicenter</td>
<td>Age range 20–85 years (mean 39.0)</td>
<td>987</td>
<td>Ramelteon 8 mg, 14 nights vs. placebo</td>
<td>A,A,A,A,A</td>
</tr>
<tr>
<td>Uchimura et al. (26)</td>
<td>Parallel, multicenter</td>
<td>Adults (mean 48.8)</td>
<td>1143</td>
<td>Placebo, Ramelteon 4 mg and 8 mg, 14 nights; then change to Ramelteon 4 mg, 8 mg and 16 mg, 14 nights</td>
<td>A,A,A,A,A,A</td>
</tr>
</tbody>
</table>

*Risk of bias (randomisation, randomisation method, drop-out or withdraw, patient blind, assessor blind, allocation concealment). A, adequate; I, inadequate; U, unclear.
Next-day residual effects
The measurement of next-day residual effects included digit symbol substitution test (DSST), immediate memory recall, delayed memory recall, level of alertness and ability to concentrate. There were totally five eligible studies (18,27,28,30,31) referred to next-day residual effects. We could not pool the data because of the heterogeneity. All these studies (18,27,28,30,31) supported that there was no differences between placebo and any ramelteon dose group in any domain of next-day residual effects.

Subgroup analysis
We did subgroup analysis of subjective sleep latency by different ages (Figure 1). For the patients from 18 to 64 years old, the reduction in subjective sleep latency with ramelteon compared with placebo was −14.26 min (−18.54 to −9.98 min; p < 0.00001; test for heterogeneity p = 0.70). Although there were no significant differences (MD −8.64 min, −17.48 to 0.20 min; p = 0.06; test for heterogeneity p = 0.76) between ramelteon and placebo in the older population (over 65 years old). In addition, there were only significant increased reports of at least one adverse effect in 8mg of ramelteon compared to placebo (RR 1.11, 1.01–1.22, p = 0.03; test for heterogeneity p = 0.75) (Figure 2).

Publication bias
We assessed the publication bias in adverse effect, which involved seven included studies. The Egger test was not significant (p = 0.60) and the funnel plot (Figure 3) did not show any asymmetry. Therefore, we concluded no potential publication bias was found.

Discussion
Conclusions for practice
Generally speaking, the efficacy and safety of ramelteon is acceptable for the chronic insomnia patients. Both subjective and PSG sleep outcomes were improved after ramelteon treatment comparing with placebo. The subjective sleep latency was reduced only in the patients of 18–64 years old, without in the patients over 65 years old. There were no differences found in the percentage of REM in PSG total sleep time between ramelteon and placebo. At the same time, ramelteon was well tolerated with no more adverse events than placebo group. And no dose–response relationships were observed, which meant no more clinical benefits were obtained from 16 mg ramelteon comparing to 4 mg. In addition, no next-day residual effects of ramelteon were found in most of studies, but it need to be further confirmed by larger sample.

Conclusions for research
More research is required for the robust conclusions, particularly well-designed; double-blind RCTs. Firstly, higher doses (32 or 64 mg) should be applied in the future investigations, considering the safety of ramelteon (17). Secondly, insomnia is more prevalent in the older population with difficulties in initiating and maintaining sleep (44). Therefore, more researches focused on this population should be in priority. Thirdly, the comparisons should be not only placebo but also the other sedative hypnotics such as zopiclone. Through the comparison with peer active

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ramelteon Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, Fixed, 95% CI</th>
<th>Mean difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18–64 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zammit 2007a</td>
<td>47.2</td>
<td>44.6</td>
<td>139</td>
<td>86.7</td>
<td>44.6</td>
<td>139</td>
<td>131</td>
<td>−14.26 [−18.54, −9.98]</td>
<td>−14.26 [−18.54, −9.98]</td>
</tr>
<tr>
<td>Zammit 2007b</td>
<td>53.9</td>
<td>43.8</td>
<td>139</td>
<td>70.2</td>
<td>43.4</td>
<td>139</td>
<td>131</td>
<td>−13.77 [−17.30, −6.24]</td>
<td>−13.77 [−17.30, −6.24]</td>
</tr>
<tr>
<td>Zammit 2007c</td>
<td>44.8</td>
<td>42.4</td>
<td>139</td>
<td>61.6</td>
<td>42.3</td>
<td>139</td>
<td>131</td>
<td>−14.55 [−18.70, −10.40]</td>
<td>−14.55 [−18.70, −10.40]</td>
</tr>
<tr>
<td>Zammit 2007d</td>
<td>54.1</td>
<td>45.2</td>
<td>139</td>
<td>86.7</td>
<td>44.4</td>
<td>139</td>
<td>131</td>
<td>−12.79 [−16.21, −9.37]</td>
<td>−12.79 [−16.21, −9.37]</td>
</tr>
<tr>
<td>Zammit 2007e</td>
<td>53.0</td>
<td>43.8</td>
<td>139</td>
<td>61.6</td>
<td>42.9</td>
<td>139</td>
<td>131</td>
<td>−14.00 [−17.00, −11.00]</td>
<td>−14.00 [−17.00, −11.00]</td>
</tr>
<tr>
<td>Zammit 2007f</td>
<td>56.2</td>
<td>45.1</td>
<td>139</td>
<td>70.2</td>
<td>43.4</td>
<td>139</td>
<td>131</td>
<td>−13.98 [−24.57, −3.40]</td>
<td>−13.98 [−24.57, −3.40]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>53.4</td>
<td>43.8</td>
<td>139</td>
<td>70.2</td>
<td>43.4</td>
<td>139</td>
<td>131</td>
<td>−14.26 [−18.54, −9.98]</td>
<td>−14.26 [−18.54, −9.98]</td>
</tr>
</tbody>
</table>

Heterogeneity: Cchr² = 9.99, df = 5 (p = 0.03), P = 9%
Test for overall effect Z = 5.63 (ν² = 0.00001)

| Age 65+ years    |                |    |       |              |    |       |        |                                  |                                  |
|-------------------|----------------|----|-------|--------------|----|-------|--------|                                  |                                  |
| Roth 2007a        | 46.2           | 45.3 | 109  | 58.2         | 45.3 | 109  | 104   | −10.06 [−12.56, −7.56]           | −10.06 [−12.56, −7.56]           |
| Roth 2007b        | 50.9           | 44.6 | 109  | 58.2         | 45.3 | 109  | 104   | −3.64 [−6.06, −1.22]            | −3.64 [−6.06, −1.22]            |
| Subtotal (95% CI) |                |    |       |              |    |       |        |                                  |                                  |
|                  | 53.0           | 43.8 | 139  | 61.6         | 42.9 | 139  | 131   | −14.00 [−17.00, −11.00]          | −14.00 [−17.00, −11.00]          |

Heterogeneity: Cchr² = 6.09, df = 1 (p = 0.01), P = 9%
Test for overall effect Z = 2.91 (ν² = 0.006)

Figure 1 Subgroup analysis of subjective sleep latency. Zammit 2007a (8 mg ramelteon, 21 nights vs. placebo); Zammit 2007b (8 mg ramelteon, seven nights vs. placebo); Zammit 2007c (8 mg ramelteon, 35 nights vs. placebo); Zammit 2007d (16 mg ramelteon, 21 nights vs. placebo); Zammit 2007e (16 mg ramelteon, 35 nights vs. placebo); Zammit 2007f (16 mg ramelteon, seven nights vs. placebo); Roth 2007a (4 mg ramelteon, two nights vs. placebo); Roth 2007b (8 mg ramelteon, two nights vs. placebo).
Figure 2 Subgroup analysis of adverse effect in different doses of ramelteon

Figure 3 Funnel plot of comparison: adverse effect
control, the efficacy and safety of ramelteon will be more plausible in the clinical application. Finally, the long-term effect of ramelteon is very significant to explore, considering the safety of ramelteon and inefficiency of benzodiazepines. As far as the present data of 6-month duration, no reduction of total sleep time or increased sleep latency is found in ramelteon as that is found in benzodiazepines (14).

**Comparison with the literature**

At present, there is only one peer meta-analysis (45) available on this subject. It was pooled analysis of 8 mg ramelteon for two nights on PSG latency to persistent sleep. In total, 566 subjects with ramelteon 8 mg and 556 subjects with placebo were included. The authors found PSG latency to persistent sleep was significantly reduced after ramelteon than after placebo. This was confirmed and extended by our subgroup analysis of ramelteon (4, 8 or 16 mg) versus placebo, PSG latency to persistent sleep was always improved in any dose of ramelteon comparing with placebo (data not shown). Actually, we prefer to discuss subjective sleep latency as the primary outcome to measure the efficacy of ramelteon, which was vacant in this reference. Regarding the safety, both of two meta-analyses agreed that ramelteon was not related to more adverse events than placebo. Although no differences of next-day residual effects were found between placebo and any ramelteon dose group in our work. However, the recent study based on the healthy population (21) found ramelteon produced significant impairment on reaction time in the Sternberg memory scanning test, slow and fast tracking, reaction speed and tracking in the divided attention test and delayed recall in the word learning test.

**Limitations of this study**

Some data in the included trials were presented in a line or column graph. This led to our inability to obtain the accurate figures of mean value and standard deviation for efficacy analysis (18,27,29). No more detailed information was acquired through inquiry. Considering the limited data available for pooled analysis, any conclusions should be cautious. We expect further investigations will be done to confirm or refute our conclusions.

**References**

21 Mets MA, de Vries JM, de Senerpont Domis LM et al. Next-day effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on highway driving performance, memory functioning, psychomotor performance, and mood in healthy adult subjects. Sleep 2011; 34: 1327–34.
28 Zammit G, Erman M, Wang-Weigand S et al. Evaluation of the efficacy and safety of ramelteon in...

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Appendix 1 MEDLINE search strategy through OVID Gateway

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi#ed,t,i,ab.
4. randomly.ab.
5. placebo.ab.
6. drug therapy.fs.
7. trial.ab.
8. groups.ab.
9. (control$ adj3 (trial or study$)).ab,t,i.
10. ((singl$ or doubl$ or tripl$ or trebl$) adj3 (blind$ or mask$ or dummy$)).mp.
11. (animals not (humans and animals$)).sh.
12. or/1–10
13. 12 not 11
15. Rozerem.tw.
16. TAK-375.tw.
17. Receptor, Melatonin, MT1.sh.
18. Receptor, Melatonin, MT2.sh.
19. ((MT1 or MT2) and melatonin and receptor$ and agonist$).tw.
21. or/14–20
22. exp Sleep.sh.
23. exp Sleep initiation and maintenance disorders.sh.
24. sleep$.tw.
25. insomnia$.tw.
26. hyposomnia$.tw.
27. wakefulness.tw.
28. egersis$.tw.
29. agrypni$.tw.
30. or/22–29
31. 13 and 21 and 30