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CHAPTER 4

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REM sleep effects as biomarker for the effects of antidepressants in healthy volunteers
Abstract

This review investigated the potential use of Rapid Eye Movement (REM) sleep effects as a biomarker for the therapeutic effects of antidepressants in healthy volunteers. A literature search was performed to select studies investigating the effects of antidepressants on REM sleep. To assess the specificity of REM sleep effects as a biomarker, the effects of other CNS drugs on REM sleep were also investigated. A significant REM sleep reduction was shown for 16/21 investigated antidepressants after single dose (mean reduction 34.1%) and for 11/13 drugs after multiple dose administration (mean reduction 29.2%). The median increase in REM latency was about 60% after single- or multiple-dose administration. REM sleep effects were linearly normalised to therapeutic doses, by dividing the REM sleep effect by the investigated dose and multiplying by the therapeutic dose. Normalised REM sleep effects were highly variable (range –27.0 to 81.8% for REM sleep and range –17.0 to 266.3% for REM latency) and showed no relationship with relevant pharmacological properties of the investigated drugs. No quantifiable dose-response relationship could be constructed after single and multiple dose administration. REM sleep effects were not specific for antidepressants. Benzodiazepines for instance caused an average dose normalised REM sleep reduction of 8.7% and a median 8.6% increase of REM latency. This review demonstrates that although REM sleep effects occur with most of the antidepressants, it is by itself of limited value as a biomarker for antidepressant action. Its specificity for antidepressants is limited, and it does not show a quantitative dose-response relationship to antidepressant agents. This is at least partly due to the complex relationships between drug pharmacokinetics and the variable time course of REM and other sleep stages throughout the night. Models that take these complex relationships into account may provide more comprehensive and quantifiable results.

Introduction

Nearly 10% of the population suffers from a depressive disorder making it one of the most common diseases of the world. Pharmacological treatments of depressive disorders include three major classes of antidepressants: selective serotonin reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors. The exact therapeutic mechanism of action of antidepressants is still not known, although the binding to specific receptors has been elucidated and most antidepressants enhance monoaminergic neurotransmission. Although antidepressant activity can be fairly reliably...
predicted from these specific pharmacological characteristics and from preclinical animal models, it remains difficult to establish efficacy in clinical practice, mainly because of the heterogeneity of the patient population, fluctuations in disease severity, and a delayed onset of antidepressant action. Consequently, it is difficult to establish therapeutic doses, and compounds can still fail in later phases of development. Therefore, efforts have been made to identify biomarkers for the therapeutic effects of new antidepressants as early as in phase I.

Some investigations have suggested that the therapeutic effects of antidepressants are caused by suppression of Rapid Eye Movement (REM) sleep. In 1975, it was suggested that antidepressants do not have a consistent effect on sleep in healthy volunteers. Since then, many more studies have been published on the possible effects of new antidepressants on sleep in healthy volunteers. The aim of this review is to investigate the relationship between different antidepressants and the effect on REM sleep in healthy volunteers and to examine the potential use of REM sleep effects as a biomarker for depression in healthy volunteers. To identify the specificity of REM sleep effects as typical biomarker for the effects of antidepressants, the effect of other Central Nervous System (CNS) drugs on REM sleep was also investigated.

**Methods**

A literature review was performed by a PubMed search (keywords: antidepressive agents, REM and healthy human) for all antidepressants. From this search, studies determining the effects on REM sleep of one or more antidepressant dose (single or multiple dose) in healthy subjects were selected. The results of all selected studies were stored in a database. To allow a quantitative comparison of study results, the reported average REM sleep effects were expressed as a percentage of the difference between REM sleep effects during treatment and REM sleep effects at baseline. Assuming linear dose–effect relationships, REM sleep effects were normalised to therapeutic dose by dividing the REM sleep effects of each antidepressant by the used dose, and multiplying the result with the therapeutic daily starting dose (for single dose results) and lowest therapeutic maintenance dose (for the multiple dose results). To determine whether relevant drug concentrations were reached during the night, the time of drug administration was compared with the expected $T_{\text{max}}$ for all single-dose studies where this information was available. The effects after single and multiple dose administration were compared to investigate potential differences in REM sleep effects during prolonged treatment.
Single dose

For each individual antidepressant, the REM sleep effects after a single dose normalised to hypothetical responses at therapeutic doses were averaged (assuming linear dose-effect relationship), to investigate the average response at therapeutic doses. Next, the relationships between REM sleep effects and specific receptor affinities were investigated. Affinity was expressed as the antidepressants’ equilibrium dissociation constant (Kd), and was obtained from the same source for all antidepressants for serotonin, noradrenaline, dopamine and muscarinic receptors. The normalised REM effects were plotted against the affinity constants of the various receptors and the specificity ratio of serotonin over noradrenaline. Finally, changes in REM sleep effects of antidepressants that are typically referred to as selective were compared to non-selective (‘classic’) agents.

Multiple dose

REM sleep effects and normalised REM sleep effects were plotted for each antidepressant individually against the number of days of administration. Normalised REM sleep effects of studies with constant repeated doses and the same number of administration days were reviewed to predict response to antidepressant therapy. Normalised REM sleep effects of different antidepressants with the same amount of days of administration were averaged and compared with each other. Finally, the same receptor affinity relationships that were investigated for single dose administration were examined.

Other CNS drugs

To assess the specificity of REM sleep effects as a potential biomarker for particularly the effects of antidepressants, a PubMed search was performed (keywords: CNS drug, REM, healthy human) to determine the effects of other CNS drugs on REM sleep.

Results

The literature search yielded 41 articles published since 1977. Twenty-four articles could be used, because some collected articles were reviews, investigated REM sleep effects in only depressive patients or effects of other drugs.
Sleep ElectroEncephaloGraphy (EEG) recordings to determine REM sleep were sometimes performed ambulantly but most frequently in a sleep laboratory. Standard sleep polygraphy was typically performed for 8 hours and daytime napping was prohibited. Most of the studies had on average two adaptation nights before the EEG recording night(s). The sleep EEG recordings were typically visually scored according to the criteria of Rechtschaffen and Kales. On average, antidepressants caused 34.1% REM sleep reduction after single dose administration and 29.2% after multiple doses in healthy volunteers. Other CNS drugs caused on average 12.2% REM sleep reduction.

**Single dose**

Twenty articles, investigating 21 different antidepressants and 45 different doses of an antidepressant, were reviewed for the effects on REM sleep after single dose administration. In the cases where this information was available (17 of 32), times of drug administration seemed to be based on the predicted $T_{max}$-values. Paroxetine was always administered in the morning before the sleep recording, which is in agreement with the long duration of action of this compound. Only fluoxetine was given relatively late ('at lights out') considering the $T_{max}$ of 4–8 hr and the accumulation of an active metabolite. In one imipramine study, a low dose was given at 21:00 hr, leading to an early peak concentration before midnight. In all other cases, the expected $T_{max}$-ranges lay between 23:00 and 03:00 hr, covering most of the normal REM sleep period.

REM sleep effects of all reported antidepressant doses are presented in Table 1. Sixteen antidepressants showed significant, consistent responses on REM sleep reduction. Inconsistent or non-significant results were reported for five antidepressant agents. Nefazodone never showed a significant reduction but rather an increase in one case and no effect in the other, consistent with previous findings in patients. REM sleep reductions that were statistically significant varied widely, from 1.8% for 100 mg trimipramine to 81.8% for 75 mg oxaprotiline. The antidepressant doses used ranged from 50% to 600% of the therapeutic dose. Consistent significant increases in REM latency were exhibited by fifteen of twenty antidepressants, although the magnitudes of the responses varied widely. The median increase of dose-normalised REM-latency for all agents was 60.1% (range -15.1% to 266%).

Twelve antidepressant therapeutic doses were administered. Eight dosages showed reduction, three showed no significant change and one dose
resulted in a significant increase of the REM sleep. This includes the mentioned two doses nefazodone (increase in one case and no effect in the other). Trimipramine 25 mg and fluoxetine 20 mg did not produce significant effects on REM sleep at therapeutic doses either. After normalising to hypothetical effects at therapeutic dose the normalised effects varied between −27.0% for trimipramine and 81.8% for oxaprotiline.

### Table 1

**Single dose antidepressants and observed REM sleep effects in healthy volunteers**

<table>
<thead>
<tr>
<th>Antidepressant (dose)</th>
<th>Reference</th>
<th>Δ REM sleep (min)</th>
<th>Δ REM sleep (%)</th>
<th>Δ REM sleep normalised (%)</th>
<th>Δ REM latency normalised (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (25mg)</td>
<td>(Nakazawa et al., 1977)</td>
<td>37</td>
<td>32.3</td>
<td>64.6</td>
<td>-</td>
</tr>
<tr>
<td>Amitriptyline (75mg)</td>
<td>(Riemann et al., 1990)</td>
<td>60.9</td>
<td>67.2</td>
<td>44.8</td>
<td>122.7</td>
</tr>
<tr>
<td>Clomipramine (50mg)</td>
<td>(Maeda et al., 1990)</td>
<td>70.3</td>
<td>80.7</td>
<td>80.7</td>
<td>266.3</td>
</tr>
<tr>
<td>Dexaxfenodone (20mg)</td>
<td>(Jobert et al., 1999)</td>
<td>55.5</td>
<td>64.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dothiepin (100mg)</td>
<td>(Wilson et al., 2000)</td>
<td>16.0 n.s.</td>
<td>19.3 n.s.</td>
<td>- n.s.</td>
<td>-</td>
</tr>
<tr>
<td>Fluoxetine (20mg)</td>
<td>(Nicholson et al., 1988)</td>
<td>9.3 n.s.</td>
<td>9.0 n.s.</td>
<td>9 n.s.</td>
<td>-17.0 n.s.</td>
</tr>
<tr>
<td>Fluoxetine (40mg)</td>
<td>(Nicholson et al., 1988)</td>
<td>3.2 n.s.</td>
<td>3.1 n.s.</td>
<td>1.5 n.s.</td>
<td>-1.8 n.s.</td>
</tr>
<tr>
<td>Fluoxetine (60mg)</td>
<td>(Nicholson et al., 1988)</td>
<td>45.9</td>
<td>44.4</td>
<td>14.8</td>
<td>8.4 n.s.</td>
</tr>
<tr>
<td>Fluoxetine (60mg)</td>
<td>(Nicholson et al., 1989)</td>
<td>36.4</td>
<td>31.4</td>
<td>10.5</td>
<td>-0.4 n.s.</td>
</tr>
<tr>
<td>Fluvoxamine (100mg)</td>
<td>(Wilson et al., 2000)</td>
<td>36</td>
<td>43.4</td>
<td>43.4</td>
<td>53.8</td>
</tr>
<tr>
<td>Imipramine (40mg)</td>
<td>(Yamadera et al., 1998)</td>
<td>49.1</td>
<td>43.8</td>
<td>27.4</td>
<td>53.1</td>
</tr>
<tr>
<td>Imipramine (75mg)</td>
<td>(Jobert et al., 1999)</td>
<td>54</td>
<td>62.6</td>
<td>20.9</td>
<td>115.3</td>
</tr>
<tr>
<td>Indalpine (25mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>55.5</td>
<td>48</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Indalpine (50mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>85.3</td>
<td>73.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Indeloxazine (40mg)</td>
<td>(Kajimura et al., 1991)</td>
<td>43.2</td>
<td>35.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lofepramine (140mg)</td>
<td>(Hopes, 1989)</td>
<td>50.6</td>
<td>56.1</td>
<td>40.1</td>
<td>85.3</td>
</tr>
<tr>
<td>Lofepramine (140mg)</td>
<td>(Herdman et al., 1993)</td>
<td>43.3</td>
<td>49.5</td>
<td>35.4</td>
<td>49.5</td>
</tr>
<tr>
<td>Maprotiline (75mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>38.1</td>
<td>32</td>
<td>10.7</td>
<td>-0.7 n.s.</td>
</tr>
<tr>
<td>Maprotiline (150mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>54.6</td>
<td>45.9</td>
<td>7.7</td>
<td>4.3 n.s.</td>
</tr>
<tr>
<td>Mianserin (20mg)</td>
<td>(Maeda et al., 1990)</td>
<td>17.6</td>
<td>16.7</td>
<td>25</td>
<td>40.1</td>
</tr>
<tr>
<td>Mianserin (20mg)</td>
<td>(Nicholson et al., 1986b)</td>
<td>33.4</td>
<td>29.9</td>
<td>44.9</td>
<td>54.1 n.s.</td>
</tr>
<tr>
<td>Mianserin (40mg)</td>
<td>(Nicholson et al., 1986b)</td>
<td>45.8</td>
<td>41</td>
<td>30.8</td>
<td>105.1</td>
</tr>
<tr>
<td>Mirtazapine (30mg)</td>
<td>(Ruigt et al., 1990)</td>
<td>-21 n.s.</td>
<td>-13.7 n.s.</td>
<td>-6.9 n.s.</td>
<td>18.2</td>
</tr>
<tr>
<td>Nefazodone (200mg)</td>
<td>(Sharpley et al., 1996)</td>
<td>14.0 n.s.</td>
<td>13.5 n.s.</td>
<td>13.5 n.s.</td>
<td>-13.3 n.s.</td>
</tr>
<tr>
<td>Nefazodone (200mg)</td>
<td>(Ware et al., 1994)</td>
<td>-24.4</td>
<td>-27</td>
<td>-27</td>
<td>-16.9 n.s.</td>
</tr>
<tr>
<td>Nomifensine (100mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>55</td>
<td>49.3</td>
<td>24.7</td>
<td>34.2 n.s.</td>
</tr>
<tr>
<td>Nomifensine (100mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>48.1</td>
<td>40.5</td>
<td>20.2</td>
<td>47.2</td>
</tr>
<tr>
<td>Nomifensine (100mg)</td>
<td>(Nicholson et al., 1986a)</td>
<td>44.9</td>
<td>38.8</td>
<td>19.4</td>
<td>-11.3 n.s.</td>
</tr>
</tbody>
</table>
Nomifensine (100mg) (Nicholson et al., 1988) | 38.9 | 37.7 | 18.8 | 1.7 n.s.
Nomifensine (50mg) (Nicholson et al., 1986b) | 25.3 | 22.6 | 22.6 | 34.8 n.s.
Nomifensine (100mg) (Nicholson et al., 1986b) | 31.9 | 28.6 | 14.3 | 18.7 n.s.
Oxaprotiline (75mg) (Gnirss, 1986) | 76.5 | 81.8 | 81.8 | 125.8
Paroxetine (20mg) (Sharpley et al., 1996) | 39.0 | 37.5 | 37.5 | 140.0
Paroxetine (20mg) (Saletu et al., 1991) | 26.6 | 34.1 | 34.1 | 102.8
Paroxetine (30mg) (Saletu et al., 1991) | 34.6 | 44.3 | 29.5 | 105.5
Paroxetine (40mg) (Saletu et al., 1991) | 42.9 | 54.9 | 27.5 | 93.2
Trazodone (100mg) (Ware et al., 1994) | 12.33 | 13.6 | 20.5 | 86.7
Trazodone (100mg) (Yamadera et al., 1998) | -10 | -8.9 | -13.4 | 14.6
Trimipramine (25mg) (Nicholson et al., 1989) | 13.6 n.s. | 11.7 n.s. | 11.7 n.s. | -0.4 n.s.
Trimipramine (50mg) (Nicholson et al., 1989) | 28 | 24.1 | 12.1 | 13.9 n.s.
Trimipramine (75mg) (Nicholson et al., 1989) | 25.1 | 21.6 | 7.2 | 11.3 n.s.
Trimipramine (100mg) (Feuillade et al., 1992) | 1.6 | 1.8 | 0.5 | 15.1
Venlafaxine (75mg) (Salin-Pascual et al., 1997) | 99.9 | 79.7 | 79.7 | -
Zimelidine (100mg) (Nicholson et al., 1986a) | 43.2 | 38.7 | 77.5 | 106.7 n.s.
Zimelidine (200mg) (Nicholson et al., 1986a) | 83.2 | 74.6 | 74.6 | 118.5

\[a \text{ REM sleep (min) after drug dose} - \text{REM sleep (min) placebo or baseline}\]
\[b \text{ (ΔREM sleep (min) / REM sleep placebo or baseline (min)) x 100 \%}\]
\[c \text{ % ΔREM effects normalised to the therapeutic starting daily dose if possible}\]
\[- \text{ unknown therapeutic starting daily dose}\]
\[n.s. \text{ not significant}\]

For ten antidepressants, two or more dose levels were investigated. As doses increased, nine antidepressants showed greater reductions in REM sleep, with the exception of trimipramine. Fluoxetine did not produce significant results at doses of 20 mg (the therapeutic dose) and 40 mg but showed significant reductions at 60 mg (300% of therapeutic dose). It was impossible to quantitatively determine dose-response relationships because of the lack of sufficient data. No clear linear dose-response relationship was observed for most antidepressants.

Table 2 shows the relationships with receptor affinities for each antidepressant. The antidepressants are presented in order of decreasing acute effect on REM sleep. The REM sleep effects plotted against the serotonin, noradrenaline and dopamine transporter affinities and muscarinic receptor affinities did not show any consistent relationship with the REM sleep effects at therapeutic dose. 5-HT/NA selectivity ratios were used to examine relationships with serotonergic selectivity, rather than absolute affinity. Zimelidine and clomipramine have higher 5-HT/NA selectivity values than many other drugs and cause the most significant REM sleep reductions.

ref. 4-6, 8, 11, 13-14, 18-21, 27
TABLE 2  Antidepressants (in descending order of normalised REM sleep reduction), equilibrium dissociation constants (Kd’s) for human serotonin (5-HT), noradrenaline (NA) and dopamine transporters and the 5-HT/NA selectivity value (from Kd values)*

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Serotonin Kd (nM)</th>
<th>Noradrenaline Kd (nM)</th>
<th>Dopamine Kd (nM)</th>
<th>Muscarinic Kd (nM)</th>
<th>5-HT/NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaprotiline</td>
<td>3900</td>
<td>4.9</td>
<td>4340</td>
<td>2900</td>
<td>0.0012</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>0.28</td>
<td>38</td>
<td>2190</td>
<td>37</td>
<td>130</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>8.9</td>
<td>1060</td>
<td>9300</td>
<td>-</td>
<td>120</td>
</tr>
<tr>
<td>Zimelidine</td>
<td>152</td>
<td>9400</td>
<td>11700</td>
<td>13000</td>
<td>62</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>4.3</td>
<td>35</td>
<td>3250</td>
<td>18</td>
<td>8.1</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>2.2</td>
<td>1300</td>
<td>9200</td>
<td>24000</td>
<td>580</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>70</td>
<td>5.4</td>
<td>18000</td>
<td>-</td>
<td>0.077</td>
</tr>
<tr>
<td>Mianserin</td>
<td>4000</td>
<td>71</td>
<td>9400</td>
<td>820</td>
<td>0.018</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.13</td>
<td>40</td>
<td>490</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>Imipramine</td>
<td>1.4</td>
<td>37</td>
<td>8500</td>
<td>90</td>
<td>27</td>
</tr>
<tr>
<td>Nomifensine</td>
<td>1010</td>
<td>15.6</td>
<td>56</td>
<td>250000</td>
<td>0.015</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>5800</td>
<td>11.1</td>
<td>1000</td>
<td>570</td>
<td>0.0019</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.81</td>
<td>240</td>
<td>3600</td>
<td>2000</td>
<td>300</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>149</td>
<td>2450</td>
<td>3780</td>
<td>58</td>
<td>16</td>
</tr>
<tr>
<td>Trazodone</td>
<td>160</td>
<td>8500</td>
<td>7400</td>
<td>324000</td>
<td>53</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>&gt;100000</td>
<td>4600</td>
<td>&gt;100000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>200</td>
<td>360</td>
<td>360</td>
<td>-</td>
<td>1.8</td>
</tr>
</tbody>
</table>

* unknown value

- ref. 1-2

* Tatsumi et al., 1997 and Richelson et al., 1984

However, fluoxetine, paroxetine and fluvoxamine also have high 5-HT/NA selectivity values, but did not cause as large REM sleep reductions as zimelidine and clomipramine. The ‘selective’ antidepressants caused REM sleep reductions ranging from 12-34%. The non-selective antidepressants amitriptyline and dothiepin showed high affinities for all investigated receptors, but they did not cause consistent REM sleep reductions, ranging from no significant effects to nearly maximum REM sleep reduction. Thus, no associations could be found between the REM sleep effects caused by antidepressants and any pattern of receptor binding affinity.

**Multiple dose**

Antidepressant effects typically develop over time, so studies using prolonged treatment were evaluated separately. Twelve articles were
included, investigating the REM sleep effects of 13 different antidepressants and 28 evaluations after multiple dose administration. Sometimes, doses were increased gradually. The final doses ranged from 50% to 210% of the therapeutic dose, and duration of treatment ranged from 2 to 25 days.

A consistent significant REM sleep reduction was observed for most drugs (11 of the 13 investigated antidepressants showed only significant results). Nomifensin 3 de die 25 mg (3dd25 mg, 150% of the therapeutic dose) for 5 days and nefazodone 2dd100 mg (67% of the therapeutic dose) for 4 days, 2dd200 mg (134% of the therapeutic dose) for 16 days and 1dd200mg for eight days and 1dd400 mg for 16 days demonstrated non-significant REM sleep effects. A significant REM sleep induction was observed after nefazodone 1dd400 mg (134% of the therapeutic dose) on day two of treatment. The significant REM sleep reductions per drug varied from respectively 17.2% for indeloxazine 1dd40 mg (unknown therapeutic dose) for 3 days and 20.9% for paroxetine 1dd30 mg (150% of the therapeutic dose) for 25 days, to 100% for venlafaxine 1dd150 mg (200% of the therapeutic dose) for 4 days. Similar results were found for REM-latency, although this was not reported in all articles. After multiple dose treatment, consistent significant increases in REM-latency were exhibited by eight of eleven antidepressants. The median increase of dose-normalised REM-latency for all agents was 62.1% (range –10.1 to 236%).

Normalisation to the hypothetical effect at therapeutic dose did not reduce the variability in significant response. The significant REM sleep reductions normalised to therapeutic dose varied from 13.9% for paroxetine 1dd30 mg (150% of the therapeutic dose) for 25 days to 91.1% for venlafaxine 1dd75 mg (at the therapeutic dose) for 2 days after multiple dose administration. Four antidepressant doses were at therapeutic dose and showed responses varying from 39.6% for fluoxetine (1dd20 mg for 6 days) to 91.1 for venlafaxine (1dd75 mg for 2 days).

For the relationship between antidepressants and REM sleep effects, each study was investigated individually, due to the wide variability in the design of the different studies. Most drugs (amitriptyline, clomipramine, imipramine, indeloxazine, lofepramine, paroxetine and dexnafenodone) caused a REM sleep reduction which diminished over time. REM-reductions did not diminish with mianserin, trazodone or venlafaxine. For most antidepressants, REM-latency-effects also diminished over time, except for trazodone and dexnafenadone. The averaged REM sleep and the averaged normalised REM sleep effects of the antidepressants with the same number of treatment days demonstrated no consistent relationship with the number of treatment days.
A dose-response relationship with a REM sleep response could not be evaluated without the confounding factor of time.

Relationships with transporter affinities of each antidepressant were only investigated for antidepressants with the same number of administration days and a constant repeated dose. Only four studies produced comparable results, which showed no relationship with any of the affinities.

**Other CNS drugs**

To obtain an impression of the specificity of REM sleep effects for (monoaminergic) antidepressant, a literature search was also performed for other CNS-active drugs. Most of these articles were on benzodiazepines (15 studies investigating 13 different benzodiazepines). The number of CNS-active drugs from other classes was too limited to get a comprehensive overview of class-effects on REM sleep. The results for 2 nonbenzodiazepine hypnotics, 2 antipsychotics and 1 antihistamine are presented for reference. The 19 articles found, together with results of a review that investigated the effects of drugs on sleep in healthy volunteers and patients published in 1996 provided the following results:

**Benzodiazepines** With the exception of 3 benzodiazepines (fosazepam, nitrazepam and doxefazepam) sleep effects of all drugs were determined after single dose administration. Fosazepam and nitrazepam were administered on two consecutive days and doxefazepam was administered for 30 days. Six (brotizolam, flurazepam, fosazepam, lorazepam, midazolam and nitrazepam) of the 13 investigated benzodiazepines caused consistent REM sleep reductions. Brotizolam and midazolam were administered at the therapeutic dose and showed 24% and 26% REM sleep reduction, respectively. Flunitrazepam (at 200, 400 and 800% of the therapeutic dose), oxazepam (50 and 83% of the therapeutic dose) and triazolam (200 and 400% of the therapeutic dose) showed both non-significant and significant REM sleep reductions in different studies. Clorazepate (at a therapeutic dose), doxefazepam (unknown therapeutic dose), nordiazepam (33 and 67% of the therapeutic dose) and temazepam (150% of the therapeutic dose), showed no significant REM sleep effects. Together with the findings of the review published earlier, it seems that about half the studies with benzodiazepines caused a REM sleep reduction (normalised to the therapeutic dose) of 8.7%, on average (range –4.5–35.0%). The median increase of dose-normalised REM-latency for all benzodiazepines was 8.6% (range –1.6% to 39.1%).
The antihistaminic agent promethazine at doses of 50 mg, 100 mg and 200 mg (above the therapeutic dose of 25 mg) showed REM sleep reductions of 21%, 35% and 45%, respectively. The non-benzodiazepine hypnotic zopiclone (at therapeutic dose) also showed a REM sleep reduction of 31%, but results for its congener zolpidem were less clear: at therapeutic doses, REM sleep reductions were significant (10%) in one study, but non-significant effects in another. The antipsychotic agent olanzapine showed non-significant REM sleep effects below therapeutic dose and a 39% REM sleep reduction at therapeutic dose. The antipsychotic pimozide (at 400% of the therapeutic dose) demonstrated no significant effects on REM sleep.

Discussion

This review aimed to systematically evaluate the use of REM sleep effects as a potential biomarker for therapeutic effects of antidepressant agents in healthy volunteers. A systematic stepwise approach to literature evaluation was adopted. Firstly, the usefulness of REM sleep effects as a biomarker was assessed by investigating the consistency of responses across various antidepressants. Secondly, the responses at therapeutic levels were determined. The effects on REM sleep of other different CNS drugs also were investigated, to get an impression of the specificity of REM sleep effects for antidepressants. Next, possible dose-response relationships were evaluated. Finally, attempts were made to relate the responses to the pharmacology of the drugs. This approach showed several links between the depression, REM sleep and monoaminergic antidepressants.

Significant reductions of REM sleep were observed with most of the investigated antidepressants, both after single (on average 34.1% normalised REM sleep reduction) and multiple (on average 29.2% REM sleep reduction) dose administration. The median increase in REM latency was about 60% after single- or multiple-dose administration. Statistically significant effects of single therapeutic doses were found in about three-quarters of all antidepressants for REM sleep and in two-thirds for REM latency. Responses generally increased with rising doses, but REM effects were too variable to identify a meaningful dose-response relationship. Statistically significant REM sleep reductions were also found for other CNS-active agents (at similar rates for benzodiazepines), but the effects were generally less consistent and smaller (on average 8.7% reduction of normalised REM sleep and median 8.6% increase of REM latency for benzodiazepines).
There are several clues for relationships between REM sleep and the pathophysiology of depression. Sleep disturbances of various types are among the most frequent symptoms of major depressive disorders. Aside from sleep continuity disturbances, sleep in depressed patients is characterised by a reduction of slow wave sleep (SWS), a reduction of REM latency, an increased amount of REM sleep, a prolongation of the first REM period and an increased number of eye movements during REM periods.

Sleep deprivation causes short-term improvement of depressive symptoms. REM sleep is regulated by a complex mechanism in the brain, which is still not completely understood but seems to involve monoaminergic activity. It is suggested that laterodorsal tegmental (LDT) and pedunculopontine (PPT) neuron activity is high and both serotonergic and noradrenergic cells have their lowest discharge rates during REM sleep. Serotonergic/noradrenergic activity is believed to suppress LDT and PPT activity and thereby reduce REM sleep. REM sleep is probably also generated, in part, by stimulation of the muscarinic cholinergic receptors in the medial pontine reticular formation. Serotonin and noradrenaline have been shown to inhibit brainstem cholinergic neurons.

Despite these biochemical links between depression, REM sleep and monoaminergic antidepressants, none of the investigated drugs evidenced relationships between their pharmacological characteristics and their REM sleep effects. Also, REM sleep effects showed a considerable overlap among different CNS-active drug classes, although the effects were generally more consistent and larger with monoaminergic antidepressants. Finally, in spite of a general increase of REM sleep reduction with rising doses, REM effects were too variable to show a meaningful quantitative dose-response relationship. These limitations thwart the practical applicability of REM sleep reduction as a biomarker during development of monoaminergic antidepressants. Nonetheless, the associations with REM sleep reduction seem stronger for antidepressants than for other CNS-active drugs. There may be many reasons why even a strong relationship would not become apparent in a literature review. One important factor is common to all the explored levels of potential relationships: the method used to quantify REM sleep reduction. Most of the reviewed articles determined REM sleep as absolute periods of time, or the percentage REM sleep within the total sleep EEG. The individual results were recalculated as percentage reduction, to allow quantitative comparisons in the current review. The hypnographic sleep recordings are typically scored by determining for each consecutive 30 second epoch, whether the subjects are awake, in REM sleep, or in non-REM sleep stages 1, 2, 3, or 4. In healthy young adults, these stages show a regular
pattern. After 80-90 minutes of non-REM sleep, the subject goes into REM sleep, which is followed by alternating cycles of non-REM and REM sleep with a period of about 100 minutes. In most hypnographic analyses, sleep stage scores are aggregated over the night, resulting in the various parameters including REM sleep duration. This makes it impossible to examine the time course of the effects on sleep and the relationships with the pharmacokinetics of the investigational drug. Most studies based their time of administration on the expected $T_{\text{max}}$ of the antidepressant agent, apparently aiming for pharmacologically active concentrations when REM sleep is most abundant. However, the individual variabilities in $T_{\text{max}}$-values and REM sleep patterns, and the constant transitions of the various sleep stages require more complex concentration-effect analyses, than are possible with aggregated REM sleep effects. For temazepam, the overall sleep effects did not show any significant pharmacokinetic/pharmacodynamic (PK/PD) relationships. Useful concentration-effect relationships were only found, after analyses with a first-order Markov mixed effect model, using the individual time-arrays of individual hypnographic 30-second epochs and each subject’s pharmacokinetic estimates. This analysis yielded descriptions of the probability of changes in sleep stages as a function of time, and quantified the influence of drug concentrations on these probabilities. Similar methods are probably needed, to show dose- (concentration)-REM sleep effect relationship, and potential correlations with the pharmacological characteristics of antidepressants. Without such complicated analyses, the practical usefulness of REM sleep reduction as a predictive biomarker for antidepressant action is limited.
REFERENCES


26 Wilson SJ, Bailey JE, Alford C, Nutt DJ. Sleep and daytime sleepiness the next day following single night-time dose of fluvoxamine, dothiepin and placebo in normal volunteers. *J. Psychopharmacol.* 2000; 14:378-386


36 van Bemmel AL. The link between sleep and depression: the effects of antidepressants on EEG sleep. *J. Psychosom. Res.* 1997; 42:555-564


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**SECTION 1: LITERATURE EVALUATION – CHAPTER 4**


68. Frank MG, Page J, Heller HC. The effects of rem sleep-inhibiting drugs in neonatal rats: evidence for a distinction between neonatal active sleep and rem sleep. *Brain Res.* 1997; 778:64-72

