Preclinical Pharmacology of Solriamfetol: Potential Mechanisms for Wake Promotion

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Table 1. TAAR1 and 5-HT1A functional activities differentiate solriamfetol from other WPA

<table>
<thead>
<tr>
<th>Drug</th>
<th>nDAT IC50 (µM)</th>
<th>hNET IC50 (µM)</th>
<th>hTAAR1 EC50 (µM) (Emax)</th>
<th>5-HT1A IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPA or nDAT/hNET inhibitor</td>
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<tr>
<td>Solriamfetol</td>
<td>3.21</td>
<td>14.4</td>
<td>10–16 (100%)</td>
<td>25</td>
</tr>
<tr>
<td>Modafinil</td>
<td>2.8</td>
<td>&gt;100</td>
<td>No dose response*</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0.26</td>
<td>2.79</td>
<td>No dose response*</td>
<td>No functional activity</td>
</tr>
</tbody>
</table>

*Data based on current studies and confirmed by published literature. **Data from published literature.

Stimulants
(+/-) Amphetamine*   0.041          0.023          2.8 (91%)          Unknown         
(+/-) Methamphetimine* 0.082          0.0013         5.3 (70%)          Unknown         

5-HT1A, serotonin 1A receptor; nDAT, half maximal effective concentration; Emax, maximal effect; hDAT, human dopamine transporter; hNET, human norepinephrine transport; hTAAR1, human trace amine-associated receptor 1.

References:

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Conclusions
• Solriamfetol activates hTAAR1, a recently recognized component of the endogenous wake-promoting system.9,7 In vitro at potencies that are within the clinically relevant plasma concentration range and overlap with observed DAT/NET inhibitory potencies.
  – No hTAAR1 activity was observed for the WPA modafinil or the DNRIs ropinirole.
• Solriamfetol shows agonist activity at the TAAR1 receptor and a lower agonist potency at 5-HT1A.
  – This activity, in addition to its established activity as a DNR, may contribute to the wake-promoting effects of solriamfetol.1,2
• Similar to known TAAR1 agonists, solriamfetol reduced the firing frequency of mouse VTA dopamine neurons in a D2-sensitive manner.
• Unlike amphetamine, solriamfetol did not promote hyperlocomotion in naive mice; hyperlocomotion in DAT-/- mice was dose-dependently inhibited by solriamfetol, similar to amphetamine.