Association of Genetic Polymorphisms with Response to Placebo Treatment in Patients with Osteoarthritis Knee Pain

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ABSTRACT

An epidemiological study with data from North Carolina suggests that the lifetime risk for symptomatic knee osteoarthritis is 44.4% in the general population, with an increase to 56.8% in patients with a history of a knee injury. The efficacy of duloxetine, a dual noradrenergic/serotonergic reuptake inhibitor, in the treatment of osteoarthritis pain has been demonstrated in 2 double-blind, placebo-controlled clinical trials. Genetic risk factors for the development of knee osteoarthritis have been identified, but no studies have examined how genetic factors might influence treatment outcome in patients with osteoarthritis knee pain.

OBJECTIVE

To test the association of potentially functional single nucleotide polymorphisms (SNPs) in several candidate genes with response to treatment with duloxetine and placebo in patients with osteoarthritis knee pain.

METHODS

• Patients and Study Design
  - Used data from a placebo-controlled clinical trial evaluating the efficacy of duloxetine and placebo in patients with osteoarthritis knee pain.
  - Patients with major depressive disorder were excluded from both studies.
  - Genomic data were obtained from 203 patients treated with duloxetine to 120 mg/day.

• Measures Used to Assess Changes in Pain
  - 11-point Likert scale patient diary
  - Brief Pain Inventory (BPI)

• Measures Used to Assess Changes in Depression
  - Beck Depression Inventory (BDI-II)
  - Hospital Anxiety Depression Scale (HADS)

RESULTS

Table 1. Factor Loading

<table>
<thead>
<tr>
<th>Depression/Factor</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II Total Score</td>
<td>0.77</td>
</tr>
<tr>
<td>HADS Anxiety Subscale Score – Odd numbered items</td>
<td>0.72</td>
</tr>
<tr>
<td>HADS Anxiety Subscale Score – Even numbered items</td>
<td>0.73</td>
</tr>
<tr>
<td>SF-36 Mental Health Transformed Score</td>
<td>0.81</td>
</tr>
<tr>
<td>SF-36 Physical Health Transformed Score</td>
<td>0.82</td>
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</tbody>
</table>

Table 2. SNPs Associated with Change in Depression Factor in the Placebo Group

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Placebo Group</th>
<th>Haplotype Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR3A</td>
<td>rs1176752</td>
<td>0.001</td>
<td>0.876</td>
</tr>
<tr>
<td>COMT</td>
<td>rs174696</td>
<td>0.001</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Figure 1. LS Mean Changes in BDI-II Total Score and Depression Factor Stratified by HTR3A SNP rs1176752 Genotype in the Placebo Group

Figure 2. LS Mean Changes in BDI-II Total Score and Depression Factor Stratified by HTR3A SNP rs1150226 Genotype in the Placebo Group

Figure 3. LS Mean Changes in BDI-II Total Score and Depression Factor Stratified by COMT SNP rs174696 Genotype in the Placebo Group

CONCLUSIONS

• Change in the Depression Factor was statistically significantly associated with rs1176752 in the Placebo Group and decreases in depression scores during treatment with duloxetine, with the strongest decreases observed in carriers of the minor homozygote genotype. Here, we observed higher baseline depression (BDI-II) scores in carriers of the minor homozygote genotype of COMT, with a trend for increase in depression scores during treatment with duloxetine in carriers of the minor homozygote genotype.

• Due to the very low level of depression observed in the current population, the clinical significance of these results require further investigation.

References:

Disclosures
This study was sponsored by Eli Lilly and Company and/or any of its subsidiaries. Drs. Fjale, Fijal, Frazier, Frakes, Gray, Piezer, Liu and Houston are full-time employees of Eli Lilly and Company and/or any of its subsidiaries. Drs. Fillingim, Smith, Diatchenko, Gracely, McLean, and Skalé are consultants and/or paid contractors to Eli Lilly and Company. The study was funded by a grant from O’stageo, a division of Osteo Biocare, Inc., a subsidiary of United Health Group.