Calming microglia: a future method for treating multiple sclerosis

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Disclosures

Will be discussing off-label use of medications

Will refer only to published scientific data

No conflicts of interest
Overview

Pathophysiology of MS

Actions of LDN in MS

Previous clinical trials of LDN

Future clinical research of LDN

Future clinical use of LDN
Overview

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Future clinical use of LDN
Overview of MS
Progression of MS

First episode → RRMS → SPMS
Central immune contribution

Ehrlich E & Mattiuz K – QIAGEN, sabiosciences.com
Degradation of blood brain barrier

Vishnu et al., 2014; Nat Rev Neuro
Peripheral immune contribution

Miller et al., 2007; Nat Rev Immunol
Overview

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The promise of LDN

Politis et al., 2012, Frontiers in Pharmacology
LDN animal testing

Rahn et al., 2011; Brain Res
Central immune-modulating effects of LDN

Liu, B et al. 2000, *JPET*
Peripheral immune-modulating effects of LDN

Duffy et al., 2014; MS Inter
Overview

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Future clinical use of LDN
# LDN and MS clinical trials to-date

<table>
<thead>
<tr>
<th></th>
<th>Size</th>
<th>Length</th>
<th>Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gironi et al., 2008</td>
<td>40</td>
<td>24 weeks</td>
<td>Primary Progressive</td>
<td>Reduction of spasticity</td>
</tr>
<tr>
<td>Cree et al., 2010</td>
<td>60</td>
<td>8 weeks</td>
<td>Relapsing-Remitting or Secondary Progressive</td>
<td>No efficacy</td>
</tr>
<tr>
<td>Sharafaddinzadeh et al., 2010</td>
<td>96</td>
<td>17 weeks</td>
<td>Mixed</td>
<td>Improvement mental scores</td>
</tr>
</tbody>
</table>


Problems with previous clinical trials

Not of long enough duration

Varying diagnostic criteria

Varying outcomes
N = 215
3.5mg LDN
Average Tx duration = 804 days
60% reported LDN improved fatigue
60% reported LDN improved disease severity
Minimal side effects

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Major goals of future clinical trials

Need to be of much longer duration
Need to use same outcomes as major trials
Need to comprehensively assess outcomes
Need to involve radiologic scans
Need to target early forms of condition
Need larger sample sizes
Need to frequently assess outcomes
Need to do dosage-finding studies
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Future clinical research of LDN

Future clinical use of LDN
Using LDN early in disease course
Adjustments of use of LDN

Dosage

Timing

Mode of administration
Future treatments based on LDN

Naltrexone analogs

Other microglia modulators

Botanicals
References

http://usa.healthcare.siemens.com/
Torres-Plates S et al., Morphometric characterization of microglial phenotypes in human cerebral cortex, *J Neuroinflammation* 2014, 11
Ehrlich E & Mattiuz K, Inflammation and neurodegenerative disease: a role of the estrogen receptor in suppression of inflammation in the brain