An Assessment by the Statin Cognitive Safety Task Force: 2014 Update

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- **No exam questions will be disclosed in my presentation.**
Outline

♦ Background
  – Task Force Members
  – Evidence grading

♦ Definition and assessment of cognition and cognitive dysfunction

♦ 2014 Questions:
  – Should a baseline cognitive assessment be performed before beginning a statin?
  – Are statins as a class associated with adverse effects on cognition?
  – What should the provider do, if a patient reports cognitive symptoms after beginning a statin?

♦ Recommendations from the panel
  – Clinicians
  – Patients
  – Future Research
Background
Cognitive Task Force Members

- Carlos H. Rojas-Fernandez BSc (Pharm), PharmD, Univ. of Waterloo, Ontario, Canada
- Larry B. Goldstein, MD, Duke University, Durham, NC
- Allan I. Levey, MD, PhD, Emory University, Atlanta, GA
- Beth A. Taylor, PhD, Hartford Hospital / Univ. of Hartford, Hartford, CT
- Vera Bittner, MD, MSPH, FNLA, Univ. of Alabama at Birmingham, Birmingham, AL

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Original Contribution


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Evidence Grading: Strength of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of recommendation</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td></td>
<td>There is high certainty based on the evidence that the net benefit** is substantial</td>
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<tr>
<td>B</td>
<td>Moderate recommendation</td>
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<tr>
<td></td>
<td>There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate</td>
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<tr>
<td>C</td>
<td>Weak recommendation</td>
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<td></td>
<td>There is at least moderate certainty based on the evidence that there is a small net benefit</td>
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<tr>
<td>D</td>
<td>Recommend against</td>
</tr>
<tr>
<td></td>
<td>There is at least moderate certainty based on the evidence that it has no net benefit or that the risks/harms outweigh benefits</td>
</tr>
<tr>
<td>E</td>
<td>Expert opinion</td>
</tr>
<tr>
<td></td>
<td>There is insufficient evidence or evidence is unclear or conflicting, but this is what the expert panel recommends</td>
</tr>
<tr>
<td>N</td>
<td>No recommendation for or against</td>
</tr>
<tr>
<td></td>
<td>There is insufficient evidence or evidence is unclear or conflicting</td>
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</table>
## Evidence Grading: Quality of Evidence

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Quality rating</th>
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<tbody>
<tr>
<td>Well-designed, well executed RCTs that adequately represent populations to which</td>
<td>High</td>
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<tr>
<td>the results are applied and directly assess effects on health outcomes</td>
<td></td>
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<tr>
<td>Well-conducted meta-analyses of such studies</td>
<td></td>
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<tr>
<td>Highly certain about the estimate of effect; further research is unlikely to</td>
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<tr>
<td>change our confidence in the estimate of effect</td>
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<tr>
<td>RCTs with minor limitations affecting confidence in, or applicability of, the</td>
<td>Moderate</td>
</tr>
<tr>
<td>results</td>
<td></td>
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<tr>
<td>Well-designed, well-executed nonrandomized controlled studies and well-designed,</td>
<td></td>
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<tr>
<td>well-executed observational studies</td>
<td></td>
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<tr>
<td>Well-conducted meta-analyses of such studies</td>
<td></td>
</tr>
<tr>
<td>Moderately certain about the estimate of effect; further research may have an</td>
<td></td>
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<tr>
<td>impact on our confidence in the estimate of effect and may change the estimate</td>
<td></td>
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<tr>
<td>RCTs with major limitations</td>
<td>Low</td>
</tr>
<tr>
<td>Non-randomized controlled studies and observational studies with major</td>
<td></td>
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<tr>
<td>limitations affecting confidence in, or applicability of, the results</td>
<td></td>
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<tr>
<td>Uncontrolled clinical observations without an appropriate comparison group (eg,</td>
<td></td>
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<td>case series, case reports)</td>
<td></td>
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<tr>
<td>Physiological studies in humans</td>
<td></td>
</tr>
<tr>
<td>Meta-analyses of such studies</td>
<td></td>
</tr>
<tr>
<td>Low certainty about the estimate of effect; further research is likely to have</td>
<td></td>
</tr>
<tr>
<td>an impact on our confidence in the estimate of effect and is likely to change the</td>
<td></td>
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<tr>
<td>estimate.</td>
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Cognition and Cognitive Dysfunction

Cognition

- Executive function
- Memory
- Language
- Visuospatial ability

Assessment Tools

- MMSE
- MoCA
- Mini-Cog / Clock draw test / Functional Activity Scale

Cognitive Dysfunction

- Minor Cognitive Impairment (MCI)
  - State of cognitive dysfunction between normal cognition and dementia
- Dementia
  - Cognitive dysfunction that involves 2 domains and is sufficiently severe to interfere with daily activities leading to a progressive loss of independence.

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Common Assessment Tools

**Mini-Mental Status Exam (MMSE)**
- Does not evaluate executive function
- Floor and ceiling effects
- Insensitive to subtle defects
- Very sensitive to educational level
- Proprietary, requires licensing fee
- Takes about 15 min

**Montreal Cognitive Assessment (MoCA)**
- 7 subscores evaluating visuospatial/executive function, naming and language, memory, attention, abstraction, and orientation
- More sensitive for MCI than MMSE
- Not established to be useful for drug-related MCI
- Takes about 15 min

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Why is it Important to Understand the Relationship Between Statins and MCI?

- Exposure to statins is large – even rare AEs affect a lot of individuals

Example:
- U.S. 2005-2008: 41% of adults 45+ years of age reported using a statin → 126 million people (based on 2010 census).*
- Assume AE incidence of 0.1% → 126,600 people affected.

Why Is It So Difficult to Assess The Literature on Statins and Cognition?

- Cognitive dysfunction is very common: 10-20% in individuals ≥65 years
- Line between MCI and dementia is often blurred
- Many different causes of cognitive dysfunction, some temporary / reversible
- Variable disease progression of dementing illnesses
- Limited F/U in case reports / case series
- Subjective cognitive complaints not evident on testing may predict future cognitive impairment

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1. Should a baseline cognitive assessment be performed before beginning a statin?

- ANSWER: No

- STRENGTH OF RECOMMENDATION: E (expert opinion)

- QUALITY OF EVIDENCE: Low

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2. Are statins as a class associated with adverse effects on cognition?

- ANSWER: No

- STRENGTH OF RECOMMENDATION: A (strong recommendation)

- QUALITY OF EVIDENCE: Low to moderate

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3. What should the provider do if a patient reports cognitive symptoms after beginning a statin?

◆ ANSWER: Cognitive testing should be conducted, other potential contributors should be ruled out, and the risk of stopping the statin should be assessed. Based on the individual patient characteristics, the statin dose could be lowered or the statin could be stopped to assess for reversibility of symptoms. If the statin is stopped, an alternative statin should be considered, preferably a statin that may be less likely to enter the brain (eg, pravastatin, rosuvastatin).

◆ STRENGTH OF RECOMMENDATION: E (expert opinion)

◆ QUALITY OF EVIDENCE: Low

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Evaluation of Patient with Cognitive Symptoms

- History from informant exam, mental status testing, physical exam
- Drugs: prescription, OTC, alcohol, substances of abuse

- Cognitive Impairment
  - Depression
  - Delirium

- MCI, Dementia

- Blood tests
  - B12
  - Thyroid
  - Organ failure
  - Neurosyphilis
  - HIV

- Imaging
  - Vascular dementia
  - Hydrocephalus
  - Tumor
  - Subdural bleed
  - MS

- Clinical features, CSF, genetics
  - Degenerative Dementias
    - Alzheimer’s disease
    - Dementia with Lewy Bodies
    - Parkinson’s disease
    - Frontotemporal lobar dementias
    - Prion disease, others
## Some Drugs Commonly Associated with Cognitive Symptoms

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Common examples*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Antimuscarinic bladder relaxant drugs: oxybutynin, tolterodine, darifenacin&lt;br&gt;Some tricyclic antidepressants: amitriptyline, imipramine&lt;br&gt;Antimuscarinic drugs for Parkinson’s disease: benztropine, trihexyphenidyl&lt;br&gt;Other antidepressants: paroxetine, mirtazapine</td>
</tr>
<tr>
<td>First-generation histamine H&lt;sub&gt;1&lt;/sub&gt; antagonists</td>
<td>Chlorpheniramine, hydroxyzine, diphenhydramine, dimenhydrinate, promethazine&lt;br&gt;Any benzodiazepine receptor agonist: diazepam, lorazepam, clonazepam</td>
</tr>
<tr>
<td>GABAergic</td>
<td>Codeine, morphine, hydromorphone, oxycodone, hydrocodone</td>
</tr>
<tr>
<td>Opioids</td>
<td>Some antipsychotics: chlorpromazine, olanzapine, quetiapine, thioridazine</td>
</tr>
<tr>
<td>Mixed mechanisms</td>
<td>GABA, gamma aminobutyric acid.</td>
</tr>
</tbody>
</table>

*Not an exhaustive list.
Recommendations To Clinicians

- In patients at risk for ASCVD, statins have important health benefits that far outweigh risks of cognitive dysfunction as a side effect.

- Cognitive side effects of statins may occur in rare individuals, the medical evidence supporting a causal effect is weak or nonexistent.

- The true incidence of these side effects cannot be determined with currently available data.

- Patient complaints about cognition should be taken seriously and appropriately evaluated, including undertaking appropriate neuropsychological testing in patients whose symptoms persist despite statin discontinuation.

- If no other causes of cognitive dysfunction are identified, discontinuation of the medication should be considered after a careful review of the benefit:risk ratio.

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Recommendations To Patients

- Cognitive symptoms have been reported by some statin users, but information from such case reports cannot be considered to be reliable, is not conclusive, and has not been proven in a cause-and-effect manner.

- Many other causes of memory complaints exist, including normal aging, the effect of many commonly used medications (e.g. sedative-hypnotics, OTC antihistamines, pain medications), and the effects of many medical conditions (e.g. anxiety, depression, sleep apnea).

- If patients have a concern about their memory or other symptoms, they should first discuss this with their health care provider before considering discontinuing their statin.

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Future Research Directions

- Studies specifically designed to assess the impact of statins on cognition
  - Need to evaluate impact of statin type / dose and effects of co-morbidities and concomitant medications.
  - Need to enroll patients representative of statin users
  - Use instruments sensitive to subtle cognitive deficits
  - Assess clinical significance of any MCI detected
  - Sufficient duration to address statin effects over time
  - Consider dechallenge / rechallenge designs

- Registry of statin users followed over many years and assessed with serial cognitive testing to assess long-term effects of statins.

- All trials involving vascular risk factor modification via pharmacological intervention ideally should include cognitive assessments.
  - The Vascular Cognitive Harmonization Statement includes a 60-min protocol that could be used in studies that require cognition to be assessed in all 4 domains.*
  - Increases cost of trials
  - Increases participant and investigator burden

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