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Conceptual Foundations of the UCSD Statin Study:

A Randomized Controlled Trial Assessing the Impact of Statins on Cognition, Behavior, and Biochemistry

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Abstract

Background—Statin cholesterol-lowering drugs are among the most prescribed drugs in the United States. Their cardiac benefits are substantial and well supported. However, there has been persistent controversy regarding possible favorable or adverse effects of statins or of cholesterol reduction on cognition, mood, and behavior (including aggressive or violent behavior).

Methods—The literature pertaining to the relationship of cholesterol or statins to several noncardiac domains was reviewed, including the link between statins (or cholesterol) and cognition, aggression, and serotonin.

Results—There are reasons to think both favorable and adverse effects of statins and low cholesterol on cognition may pertain; the balance of these factors requires further elucidation. A substantial body of literature links low cholesterol level to aggressive behavior; statin randomized trials have not supported a connection, but they have not been designed to address this issue. A limited number of reports suggest a connection between reduced cholesterol level and reduced serotonin level, but more information is needed with serotonin measures that are practical for clinical use. Whether lipophilic and hydrophilic statins differ in their impact should be assessed.

Conclusion—There is a strong need for randomized controlled trial data to more clearly establish the impact of hydrophilic and lipophilic statins on cognition, aggression, and serotonin, as well as on other measures relevant to risks and quality-of-life impact in noncardiac domains.

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are important and widely prescribed drugs, with incontrovertible cardiac benefits. Nevertheless, there are questions regarding whether statins may cause noncardiac effects, including central nervous system (CNS) effects, that may have important consequences. This article describes the conceptual foundation for the University of California, San Diego (UCSD) Statin Study, a double-blind, placebo-controlled study funded by the National Heart, Lung, and Blood

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Institute, an institute of the National Institutes of Health, that seeks to address the impact of statins on cognition, behavior, serotonin, and other noncardiac indexes.

In this randomized controlled trial (RCT), 1000 subjects will be randomized equally to receive pravastatin sodium, 40 mg; simvastatin, 20 mg; or placebo for 6 months, and will receive a postdiscontinuation follow-up visit at 8 months. Eligible subjects are men 20 years or older or postmenopausal women with low-density lipoprotein cholesterol levels of 115 to 190 mg/dL (3.0–4.9 mmol/L). Subjects with existing cardiovascular disease or diabetes mellitus, or with contraindications to receiving statin treatments, are not eligible for enrollment. We hypothesize that statins may lead, on average, to reductions in cognitive function and increases in irritability, and that effects on irritability (if any) may be mediated by reductions in central serotonin levels. Primary end points include a composite cognitive measure including the Elithorn Maze, Grooved Pegboard Test, Digit Vigilance Test, and Recurrent Words; an aggression measure, the Point Subtraction Aggression Paradigm; and whole blood serotonin level, which is inversely related to central serotonin level. All hypotheses will receive 2-sided testing.

Statins have major benefits to heart disease and nonfatal stroke[1,2] and are widely considered to have a favorable safety profile.[3] The top-selling statin sold between $7 billion and $8 billion in 2002 and is projected to increase sales to $10 billion in 2003.[4,5] Statins were cited as major contributors to the 17% increase in costs for prescription drug use in 2001[6] and have included the number 1 and 2 most prescribed drugs worldwide.[7] Further increases are expected in the wake of recent revisions of lipid-lowering guidelines, which are expected to triple statin use to approximately 36 million users[8]; additional increases are anticipated from the subsequent Heart Protection Study finding that no cholesterol level is too low for cardiovascular benefit to be reaped in those at cardiovascular risk,[9] which may extend treatment to those with “favorable” lipid profiles. Media reports quote experts as asserting that statins are so effective and so safe that they should be “put in the water supply.”[8,10,11]

As the very real cardiovascular benefits of these drugs are spawning dramatic expansion of those eligible to receive them, the need to more fully understand the full range of effects of statins, including effects on noncardiovascular outcomes—both favorable and adverse—becomes more urgent. Indeed, recently concerns regarding statin noncardiac effects have been heightened in the wake of (1) market withdrawal of cerivastatin sodium (Baycol) because of fatal rhabdomyolysis,[12] leading to the joint American College of Cardiology–American Heart Association–National Heart, Lung, and Blood Institute advisory[13]; (2) recent confirmation that myopathy that does not elevate creatine kinase level occurs with statins and is demonstrable on biopsy[14]; and (3) recent demonstration of a 16-fold excess risk of peripheral neuropathy associated with statin use.[15,16] Cognitive issues have assumed special importance. Media reports have highlighted postulated benefits of statins to cognition (eg, NBC Nightly News, March 14, 2002), based on observational findings.[1,2] Nevertheless, these possible observational benefits appear to be contravened by findings from a small randomized study, in which lovastatin was associated with modest reductions in cognitive function relative to placebo.[3] These discrepancies, among others, underscore the need for high-quality randomized trial data to help address and resolve uncertainties in noncardiac and particularly central effects of statins. Clearly, continued identification of

important noncardiac benefits and risks of statins mandates renewed efforts to understand the full scope of statins effects, favorable[9,17] and adverse. Only then can a reasoned approach to risk-benefit assessment be applied to clinical decisions to commence or continue statin treatment.

This report reviews the conceptual issues that underlie the UCSD Statin Study, a randomized trial that will compare equipotent low-density lipoprotein–lowering doses of simvastatin (20 mg), pravastatin sodium (40 mg), and placebo in a total of 1000 subjects, examining noncardiac end points emphasizing, but not confined to, CNS-related issues, including cognition, behavior, and serotonin biochemistry.

THE ISSUES

CHOLESTEROL, STATINS, AND COGNITION

Favorable Statin Effects—Mechanisms by which statins may affect cognition favorably have been proposed.

Cholesterol appears to play a role in β-amyloid production in Alzheimer disease (AD), and blockade of cholesterol production by statins has been theorized to protect against AD.[18] Two observational studies have reported that patients taking statins have lower rates of AD,[1,2] and studies have shown that those with AD may have higher cholesterol levels. Older elderly patients with AD have higher cholesterol levels than older elderly patients with other dementias[19] and than those without dementia.[20] The ε-4 genotype of apolipoprotein E, which is linked to AD and also to vascular dementia, is associated with elevated lipids levels.[21]

Statins protect against nonfatal (though not fatal) stroke,[1,2] perhaps in part through reductions in blood pressure (see sixth paragraph of “Counters to Favorable Statin Effects, and Adverse Statin Effects”), antithrombotic effects,[22,23] and augmentation of endothelial nitric oxide with enhanced cerebral perfusion,[24–26] and stroke or cerebrovascular ischemia is a major contributor to cognitive loss in the elderly. (The more severe manifestations of ischemic cognitive loss are widely recognized and are termed *multi-infarct dementia*). Through these mechanisms, statins could protect cognitive function with aging. However, the apparent link between statin use and lower rates of AD in observational studies need not imply that statins protect; first, those treated with statins have higher cholesterol levels before, and often despite, treatment.[10] Statin users were also noted to have higher rates of transient ischemic attacks in one of those studies,[27] yet one could not assert that statins cause transient ischemic attacks, and indeed randomized trial evidence shows that statins protect against them,[2,28] a reminder that observational findings may be in opposition to results from randomized trials.

In addition, statins are costly drugs more often received by persons of higher education or socioeconomic status, which in turn is associated with reduced incidence of AD. (This may be because it takes less time for the effect of AD, if present, to be perceived.[29] Head injury and lower intellect from any cause are also linked to increased risk of diagnosis of AD during life.[29,30])

On the other hand, there is also evidence that AD is associated with higher cholesterol levels. The finding that older elderly patients with AD have higher cholesterol levels than older elderly patients with other dementias[19] could partially reflect a contribution by low cholesterol level to non-AD mechanisms for cognitive decline. In addition, although AD is associated with higher cholesterol level than that in a normal comparison group, high cholesterol level could be a noncausal[31] concomitant of genotypes that predispose to AD, such as that associated with the ε-4 isoform of apolipoprotein E.[21]

Counters to Favorable Statin Effects, and Adverse Statin Effects—Deleterious effects on cognition have also been proposed, and some of the evidence for benefit can be countered. Cholesterol serves vital functions in the brain. The CNS accounts for only 2% of the body mass, but nearly a fourth of nonesterified cholesterol.[32] Glial-derived cholesterol has recently been shown to be vital for formation of synapses, the connections that allow nerve cells to communicate and contribute to memory and cognition.[11] In addition, cholesterol is a major component of myelin, the material that provides the insulation for the axons that permit nerve cell communication to occur, and that ensures proper fidelity and timing of signal transmission.[33–36] Cholesterol is the precursor to all steroid hormones, which serve both peripheral and central communication functions (there are steroid hormone receptors in the brain, including particularly in areas important for memory function, such as the hippocampus[37,38]—as well as areas important for behavior, such as the amygdala). Cholesterol is an important component of all membranes and has roles in transmembrane exchange, enzyme function, and regulation of receptor expression, including neurotransmitter receptors.[12]

Cholesterol is involved directly in mitochondrial function and cellular respiration and energetics,[39–42] and indirectly through its effect on coenzyme Q10 (CoQ10). Low cholesterol level is associated with low CoQ10 level, and statins produce a dose-dependent reduction in CoQ10 concentrations.[43–45] Coenzyme Q10 is needed for mitochondrial function, cellular respiration, and energy production.[46–49] The brain consumes a large fraction of the oxygen and energy used by the body, and inadequate energy supply to meet demand may lead to cell death.[49] Low CoQ10 levels have been linked to encephalomyopathies.[47,48,50]

As a perhaps minor mechanism, cholesterol protects against adverse effects of certain toxins including pesticides[51–53] and organic solvents,[54] which have been linked to Parkinson disease,[55–60] with its dementing element. Various mechanisms could contribute to this protection. First, cholesterol protects against membrane fluidization by pesticides[60] and sustains barrier function.[54] Second, cholesterol transports key enzymes that metabolize pesticides, such as paraoxonase[61–64]; low paraoxonase activity, in addition to low-metabolizing paraoxonase genotypes,[65] has been clearly linked to illness with neurocognitive symptoms in both sheep dippers and ill Gulf War veterans, many of whom were exposed to carbamate and organophosphate agents.[66–70]

Some observational studies suggest adverse cognitive effects of low cholesterol level, which has been linked to increased evoked potential latencies[13] and to subsequent cognitive decline.[14] Other studies suggest that cholesterol level correlates positively with mental

processing speed or general mental efficiency, and in older individuals, relatively higher cholesterol level has been associated with relative preservation of cognitive function and behavior,[15–18] as well as decreased mortality.[71]

Some studies have suggested statin-related cognitive adverse effects. Several small-sample (<25 per group), short-duration (4–6 weeks) studies have not shown cognitive effects,[19–21] although one did report lovastatin-associated cognitive deterioration measured by demanding tests of attention in normocholesterolemic men.[72] However, a randomized trial of longer duration (6 months) and larger size (n = 192) found that lovastatin (20 mg) vs placebo reduced performance on tests of attention (P = .03) and psychomotor speed (P = .03).[73] Individuals in the treatment group experiencing the most consistent performance decrements (the large-decrement quartile of the treatment group vs the other 3 quartiles) had lower pretreatment cholesterol levels (252 vs 267 mg/dL [6.5 vs 6.9 mmol/L]; P = .05) and lower posttreatment cholesterol levels (191 vs 216 mg/dL [4.9 vs 5.6 mmol/L]; P = .002).

Several studies, observational and experimental, have linked statin use in people and animals to lower diastolic, or diastolic and systolic, blood pressure.[74–79] For those with hypertension, this mechanism could assist in cognitive protection (via reduced stroke risk from improved blood pressure control). However, according to observational studies, lower diastolic (and perhaps systolic) blood pressure, to the contrary, disposes to accelerated cognitive decline, depression, and worsened mortality in older elderly.[80–89] Conceivably, then, the older elderly, as well as persons with low blood pressure, marked nocturnal dipping of blood pressure, or autonomic dysfunction with episodes of relative hypotension, could be subject to enhanced risk of ischemic damage to perfusion-dependent cerebral tissue.[90–92] This mechanism would, if verified, provide one mechanism of cognitive loss (or cognitive preservation) independent of whether a drug crosses the blood-brain barrier.

Some subjects report memory problems attributed to statins,[93,94] and our UCSD Statin Study Group has received scores of reports of memory disturbance attributed to statins. These reinforce the need for a formal trial to evaluate the impact of statins on cognition, to evaluate whether cognitive benefit, cognitive decline, or both may occur with these drugs.

The present study seeks to replicate and extend previous findings, with commonly used statins (simvastatin and pravastatin) chosen to represent the extremes of the lipophilicity spectrum. Simvastatin is the most lipophilic and pravastatin the most hydrophilic among marketed statins, with pravastatin exerting its effect through active selective uptake into the liver.[95–103] This will permit assessment of whether relative blood-brain barrier penetration has an influence on cognitive benefits or detriments, if any, associated with statin use.

CHOLESTEROL, STATINS, AND AGGRESSION OR VIOLENCE

The literature pertaining to the link between low or lowered cholesterol level and violence and serotonin has been reviewed elsewhere.[104] Low cholesterol level has been associated with excess violent death or death from suicide in prospective community cohort studies (after adjustment for potential confounders), including the largest studies.[105–109] The excess in suicide appears to be disproportionate, in risk ratio, to any increase in depression (which has been, at best, variably supported), and may result from an increase in follow-through on

suicide behaviors for the same level of depression. Low serotonin level is the hypothesized mediator between low cholesterol level and violence,[104] and the low-serotonin state has been conceptualized by some as reflecting a reduction in harm avoidance. This relationship has been cited in a number of studies[110,111] and may relate to discrepancies in serotonin links to depression vs suicide.[112] If this is accurate—if 2 groups have equal depression and contemplation of suicide, but one group has reduced inhibition of harmful impulses—this group may manifest more harmful behaviors irrespective of whether there is an increase in depression.

In the largest prospective cohort study performed that has explored these issues, low cholesterol level was not associated with subjective depressive symptoms on follow-up but was strongly linked to death from suicide.[108] A lesser but significant link to hospitalization for major depression was seen, and could be speculated to result in part or in whole from suicidal behaviors leading to such hospitalization.

There is one apparently contradictory study, linking high cholesterol level to suicide in a Finnish population[113]; however, Finland has the highest national alcoholism rate, and unpublished analyses conducted by one of us (B.A.G.) in concert with Helsinki Heart Study researchers (Leena Tenkanen, PhD, and colleagues) and Sarnoff Mednick, DrMed, PhD, from the University of Southern California, Los Angeles, showed that in Finnish subjects, there was a potent positive link between alcohol consumption and cholesterol level (since alcohol increases levels of high-density lipoprotein and very-low-density lipoprotein cholesterol), so that any grouping in alcohol measurement or any measurement error in alcohol consumption will be expected to produce the spurious appearance of a link between higher cholesterol level and violence. (Tanskanen et al did not state how their alcohol data were coded and did not cite this possibility as a source of their finding. Reanalysis adjusting for the same variables as in the study by Partonen et al[108]—although again the coding of these variables was not disclosed—still led to a positive link, although it lost statistical significance.[113,114]) In our analysis, among nondrinkers, the expected direction of link between cholesterol level and suicide was upheld, with a 2-fold excess of suicide in those with cholesterol levels below the population median, although there were comparatively few nondrinkers and the effect did not reach significance.

A prospective cohort study (cholesterol measurement preceded data on violent outcomes) using the large Varmland, Sweden, database merged with national Swedish computerized databases on arrests, mortality, education, and alcohol, as well as demographic factors, also showed an increase in arrests for violent crimes against others, adjusted for potential confounders.[115] Among observational (cross-sectional and case-control) studies in psychiatric and criminal populations, most have shown a statistically significant link between low cholesterol level and increased risk of suicide behaviors or aggressive behaviors,[116–128] and none showed a link in the other direction. (A link to suicide ideation was not seen in a study that found a link to suicide behaviors, potentially consistent with one theory of low serotonin state, conceptualizing it as primarily a reduction in harm avoidance.[110])

Suggesting possible causality in such relationships, 2 studies have shown that reducing cholesterol level experimentally in nonhuman primates is associated with increased aggression against conspecifics (ie, others of their species), relative to aggression rates in those not assigned to cholesterol reduction.[129–131] This complements observational information linking cholesterol and aggression in primates.[132] In addition, 4 of 8 (nonindependent) meta-analyses of prestatin RCTs of lipid-lowering drugs found a significant association between cholesterol reduction and violent death,[133–138] perhaps selectively in men and in primary prevention.[104] The meta-analyses favoring the association included the studies with the most appropriate inclusion and exclusion criteria—including all and only unifactorial RCTs. There is some suggestion that the effect may be preferentially evident in those with risk factors for aggression, such as psychiatric history, alcohol use, and noncompliance,[139] as should be expected. The same change in relative risk, applied to those at higher baseline risk, produces a greater change in absolute risk—whether for violent outcomes or heart disease, where the same finding is well recognized.[140]

Despite these findings, statin RCTs and meta-analyses have not shown a relationship, or even a substantial trend, toward increased violence or violent death. While this might be interpreted to extinguish the question (since statins are potent cholesterol-lowering agents), the issue remains unresolved, in part because of failure to select for those at risk or to include morbidity or sensitive measures of behavior.

CHOLESTEROL AND SEROTONIN

Several studies in humans and primates suggest a specific connection between low or lowered levels of fats or cholesterol and low or lowered serotonin activity.[130,141–145] Two observational analyses in humans found a positive relationship between cholesterol level and, in this case, peripheral serotonin levels, of “borderline significance” in one study ($P = .059$)[144] and significant in a better-designed analysis ($P<.05$).[104,145] Most persuasively, because of the experimental nature of the studies, monkeys assigned to diets leading to lower cholesterol levels have been shown to exhibit significantly lower brain serotonin activity.[130,142] Golomb and colleagues[146] published a possible mechanism by which lower cholesterol level may be associated with reduced serotonin production.

Meanwhile, a large body of literature supports a causal link between low or lowered central serotonin activity and aggressive or impulsive behavior in humans and animals.[147–150] Animals (including primates) with low or lowered serotonin levels are more aggressive, whether serotonin is reduced by depleting the precursor tryptophan,[151–153] competitively inhibiting tryptophan hydroxylase (the rate-limiting enzyme in serotonin production),[154,155] creating lesions in serotonin-producing areas,[156,157] poisoning serotonergic neurons,[155,158,159] or genetically engineering animals devoid of serotonin 1b receptors.[160] Raising low serotonin levels, or restoring lowered serotonin levels, returns aggressive animals to a more sanguine disposition.[161–163] In humans, low brain serotonin level (by cerebrospinal fluid 5-hydroxyindoleacetic acid or hormonal measures) is linked to increased aggression, suicide, homicide, and arson.[149,164–167] Serotonergic drugs have reduced aggressive behaviors in violent institutionalized humans.[168–173]

Residual uncertainty attaches to whether or to what degree cholesterol relates to serotonin in humans and whether cholesterol reduction leads to changes in serotonin activity. Information pertaining to this is clearly important and will be addressed in this study.

CARDIOVASCULAR REACTIVITY

Low baseline heart rate and extremes of cardiovascular reactivity may be predictors of aggression. Cardiovascular reactivity has been linked to risk of aggressive behaviors[174]; aggressive youths and adults have low resting heart rates[175,176] and may have low heart rate response to aggressively challenging situations,[176,177] although other groups of aggressive individuals have been shown to have high heart rate response to challenge.[176] (Some literature suggests that there are 2 types of aggression, differing in motivation and biological underpinnings; one relates to underarousal and low cardiovascular reactivity, while the other relates to overarousal and is expected to be linked to high cardiovascular reactivity.[178]) In addition to heart rate differences, low ephinephrine and high norepinephrine levels during stressor anticipation and high norepinephrine-epinephrine responsiveness may serve as markers for aggression-prone individuals.[179,180] Thus, low epinephrine levels and high norepinephrine-epinephrine ratio are associated with a subset of criminal offenders more likely to have committed violent personal attacks.[179–181] Anticipation of stress led to particular increases in norepinephrine-epinephrine ratio in such subgroups.[181] Thus, differences in baseline catecholamine levels and cardiovascular reactivity could indicate different susceptibility to aggression. Moreover, some evidence suggests that lipids may affect the catecholamine system: dietary fat composition alters uptake of catecholamines by cerebral cortex,[182] and cholesterol induces changes in adrenergic sensitivity.[183] Dietary cholesterol and fatty acids influence catecholamine-induced adenylate cyclase activity.[184,185] Furthermore, there is evidence of an effect of lipids on cardiovascular reactivity in some subjects.[186] Thus, there is reason to assess whether cardiovascular reactivity will be altered by assignment to statin treatment, as well as to evaluate whether cardiovascular reactivity status relates to susceptibility to adverse behavioral effects of statins.

ADVERSE EFFECTS IN THE DETERMINATION OF WHO IS TREATED

Examination of adverse effects of cholesterol reduction, such as the possible effect on violence, is an integral part of identifying who merits cholesterol-lowering treatment. The ultimate unit of interest in examining outcomes of clinical studies must be the patient as a whole, not a disease—even one as pervasive as cardiovascular disease. Ideally, overall morbidity and mortality should be evaluated, yet no RCT has looked at overall morbidity, only at cardiac morbidity. Studies have examined overall mortality. Patients at high risk of death from heart disease have been shown to have reduced overall mortality with cholesterol reduction, as has been demonstrated in the Scandinavian Simvastatin Survival Study,[187] in meta-analysis of statin studies in secondary prevention,[2] and in meta-analysis of nonstatin studies involving high-risk patients.[188] In contrast, patients at low risk of death from heart disease have been found to be significantly harmed, in overall mortality, in meta-analysis (a significant 22% increased odds of deaths was found[188]). These studies did not include recent statin trials. Statins, because of multiple other effects possibly independent of lipid reduction that may be beneficial to cardiovascular disease,[189–206] are likely to have a different risk-

benefit profile.[2] Nevertheless, the statin trials in the lowest cardiovascular risk populations still have failed to suggest mortality benefit, with trends, if any, toward harm.[207,208]

Because current guidelines advocate screening and treatment not only in those at high cardiovascular risk, this absence of benefit—or suggestion of harm—in low-risk patients cannot be dismissed as clinically irrelevant. Efforts to characterize and understand (or exclude) potential negative and positive effects of cholesterol reduction are important. Understanding these effects may permit identification of individuals susceptible to selected adverse outcomes. Understanding such effects may facilitate more informed risk-benefit decisions. Therefore, continued investigation of the possible effect of cholesterol reduction on adverse and favorable cognitive and behavioral outcomes is vitally important.

OTHER END POINTS

Unresolved issues remain pertaining to statin effects on other noncardiac end points, including sleep[96,209–211]; muscle[212–222]; glucose and insulin; and blood pressure. Statins lower CoQ10 levels,[223–225] which may adversely affect blood glucose[226,227] and blood pressure,[228] and animal studies suggest blood pressure–increasing effects of statins in hypertensive rats.[229,230] However, some studies suggest a link of statins to lower rates of diabetes mellitus[231] and to reduced blood pressure.[75–77] Anxiety and stress produce catecholamine release, which raises cholesterol levels through hemoconcentration,[232,233] and high cholesterol level indeed attends anxiety disorders.[234–239] High comorbidity between depression and anxiety can confound associations between cholesterol and depression, and this merits study. These factors suggest that measures of blood pressure, blood glucose, and anxiety merit additional study in randomized trials.

COMMENT

Although cholesterol is well represented in the brain and other tissues, a dearth of research has formally examined CNS and other noncardiac effects of statins, using high-quality study methods. The findings summarized here show the strong need for RCT data to better define the impact of statins on a range of noncardiac end points, emphasizing but not confined to CNS outcomes. These should examine the impact of statins, by lipophilicity, on cognition, irritability or behavior, and serotonin, as well as secondary outcomes of cardiovascular reactivity, blood pressure, and mood. Regarding cognition, statins reduce the risk of stroke[1,2] and may or may not reduce the incidence of AD,[240–242] but cholesterol is integral to myelin sheaths and essential to synapse formation, and some evidence suggests deleterious effects on cognition.[70] There remain concerns that warrant investigation of whether statins may, perhaps in a susceptible subset, have effects on irritability or aggression, because many reports not focusing on statins favor effects of low or lowered cholesterol level on increased irritability, suicide, or aggression. Although existing RCTs of statins have not supported an effect of statins on violence (confined to evaluation of violent death), the nature of the outcomes examined and subjects selected limit the authority with which an effect can be excluded. Some reports suggest a link between lowered cholesterol level and low serotonin concentrations, providing a possible mediating factor for irritability or aggression and suicide attempts. A possible mechanism for such an effect on serotonin

has been proposed. A sizable RCT examining the effect of statins on cognition, behavior, and serotonin is needed to provide higher-quality evidence to support or discredit causal effects on these outcomes.

Statins have become the most widely prescribed drugs, and their use continues to increase. In this context, it is increasingly urgent that work be undertaken to better understand the full range of effects of these drugs, noncardiac as well as cardiac, adverse as well as favorable, as a function of patient characteristics. Only through such study can we determine who, during treatment, should be monitored with particular care. Only through such study can benefits and tradeoffs of treatment be more fully defined. Only by defining those tradeoffs can patients' health state preferences be effectively considered in treatment decisions.

In light of mounting inconsistencies in the literature pertaining to the direction and importance of central and peripheral effects of these drugs, there is new urgency attending the need to obtain high-quality RCT evidence examining the link of cholesterol level to cognition, aggressive or irritable behavior, and other noncardiac effects. The UCSD Statin Study, a National Institutes of Health–funded RCT, will take critical steps toward addressing these issues.

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