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Influence of Baseline Psychological Health on Muscle Pain During Atorvastatin Treatment

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Abstract

Background—HMG-CoA reductase inhibitors (statins) are generally well-tolerated, with statin-associated muscle symptoms (SAMS) the most common side effect (~10%) of statin users. However, studies and clinical observations indicate that many of the self-reported SAMS appear to be non-specific (i.e., not attributable to statins).

Objective—Mental health and wellbeing influences self-perception of pain, so we sought to assess the effect of baseline wellbeing and depression on the development of muscle pain with 6 mo of atorvastatin 80mg/d (ATORVA) or placebo in healthy, statin-naïve adults

Methods—The Psychological General Well-Being Index (PGWB; n=83) and Beck Depression Inventory (BDI; n=55) questionnaires were administered at baseline in participants (aged 59.5±1.2yr) from the STOMP trial (#NCT00609063). Muscle pain (Short-Form McGill Pain Questionnaire [SF-MPG]), pain that interferes with daily life (Brief Pain Inventory [BPI]), and pain severity (BPI) were then measured before, throughout, and after treatment.

Results—At baseline, there were no differences in wellbeing (PGWB), depression (BDI), or pain measures (SF-MPG and BPI) (ps 0.05) between placebo and ATORVA groups. Baseline wellbeing correlated with baseline BPI pain severity (r=−0.290, p=0.008). Baseline depression correlated with baseline pain (SF-MPG; r=0.314, p=0.020). Baseline wellbeing and depression did not predict the change in pain severity or interference after 6 mo among the total sample or between groups (ps 0.05).

Conclusion—Baseline wellbeing and depression were not significant predictors of pain after 6 mo of ATORVA (ps 0.05). Thus, they do not appear to increase the risk of SAMS in otherwise healthy adults.

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Conflicts of Interest:

For all remaining authors none were declared.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States (US), affecting 1 in 3 (or 81.1 million) adults¹. Lowering low density lipoprotein cholesterol (LDL-C) by 1mmol/L through lifestyle or pharmacological intervention reduces CVD related events by 22%². Hydroxy-methyl-glutaryl CoA (HMG CoA) reductase inhibitors, or statins, are the most effective pharmacologic therapy to lower LDL-C as they have the potential to decrease LDL-C up to 60% and lower overall CVD risk by ~50%³. In addition, 25% of Americans 45 yr or older are currently prescribed a statin, making statins the most widely prescribed drugs in the US and the world^{3,4}.

Statin are generally well tolerated; however, patient surveys indicate 30–62% of statin-prescribed patients discontinue therapy due to muscle fatigue, weakness and muscle pain complaints^{5–7}. Incidence of statin-associated muscle symptoms (SAMS) ranges widely from 10–25% in non-industry funded clinical trials^{8–10} to 60% in observational studies⁵. In addition, recent studies indicate that 30–50% of patients with SAMS actually experience non-specific muscle pain; that is, pain unrelated to the statin drug^{11–13}. Therefore, it difficult to diagnose and treat SAMS, identify statin users who may be at risk for SAMS prior to therapeutic initiation, and effectively treat CVD with statins¹⁴.

Although the pathological mechanisms underlying SAMS are not well understood¹⁴, differences in psychosocial characteristics of statin users may affect the frequency of SAMS such that individuals who are more depressed may *feel* more pain. For example, patients with fibromyalgia-like symptoms are three times more likely to have SAMS, while treatment with antidepressants for 3 mo reduces SAMS by 50%⁸. These results suggest that mental health may influence self-perception of pain and may contribute to the high incidence of non-specific muscle pain in statin users. Therefore, we sought to assess the effect of psychological health on muscle pain before and after 6 mo of atorvastatin 80 mg/d (ATORVA) or placebo in healthy, statin-naïve adults. “Psychological health” was operationalized in the present study through measurement of wellbeing and depression. We hypothesized that lower levels of wellbeing and higher levels of depression at baseline would result in higher muscle pain severity and pain interference with quality of life (QoL) after statin therapy.

Methods

Study Overview

The present study is part of a larger clinical trial, “The Effect of Statins on Skeletal Muscle Function and Performance,” of which the methods have previously been published in detail (STOMP; NIH R01HL081893-01A2)^{9,15}. STOMP was the first randomly assigned, double-blinded study designed to examine the incidence of SAMS. SAMS was defined as pain that was new unexplained, persisted, went away upon 2 weeks of statin dechallenge and resumed upon 4 weeks of statin rechallenge¹⁵. Briefly, 420, statin naïve, healthy men and women were randomized to atorvastatin 80mg (ATORVA) or placebo for 6 mo. At baseline, a subset of patients from the larger STOMP trial (n=83) were administered questionnaires to determine whether baseline depression and psychological wellbeing were related to SAMS

(Figure 1). This subset represents those enrolled in the present study. The Hartford Hospital Institutional Review Board approved the study protocol (IRB #THOM002069HE), and written informed consent was obtained from all participants.

Measures

Psychological Wellbeing—The Psychological General Wellbeing Index (PGWB) is a 22-item, validated questionnaire which produces a self-perceived evaluation of psychological wellbeing expressed by a summary score ranging from 0 (poor) to 110 (good)¹⁶ and six affective states: anxiety (range 0–25), depressed mood (range 0–14), sense of positive well-being (range 0–20), self-control (range 0–15), general health (range 0–15), and vitality (range 0–20) (15). Higher scores on each of the relative ranges within the six affective states indicate “low”/“good” sub-group scores, while low scores indicate “high”/“poor” sub-group scores. For example, higher ranges within the anxiety state (range 0–25) indicate “not bothered by nerves; low tension; not anxious”, while lower scores indicate “extremely bothered; very tense; and anxious”. The PGWI is a commonly used and validated questionnaire to measure wellbeing and QoL in both the general population and in special populations with an internal consistency of 0.94 and high internal reliability of 0.92 to 0.96^{17,18}. The six affective states also have been shown to have high internal reliability with a retest reliability of 0.80 to 0.92^{17,18}.

Depression—The Beck Depression Inventory (BDI) is a 21 question assessment of depression severity which produces a summary score ranging from 0 to 63 with cut-off points used to indicate the severity level of depression¹⁹. A summary score >20 on the BDI is considered clinical depression while a summary score <13 indicates minimal depression. BDI is one of the most widely used, validated instruments for the detection of depression in general populations with an internal consistency of 0.9 and retest reliability of 0.73 to 0.96²⁰.

SAMS—Muscle pain was quantified at baseline and on a biweekly basis throughout the study through administration of standardized questionnaires. The Brief Pain Inventory (BPI) is a nine-item measure of pain severity and the extent in which pain interferes with QoL²¹. A pain severity score is calculated by averaging scores on four pain-intensity items, and a pain interference score is calculated by averaging scores on seven pain interference items to determine the extent to which the muscle pain interferes with two domains of daily functioning: **activity** (i.e., general activity, walking ability, normal work) and **affective** (i.e., mood, relations with other people, sleep, enjoyment of life). Although the BPI was originally developed to assess cancer-related pain, it has been validated for use with nonmalignant pain populations and is used widely used in both clinical and research settings. In non-cancer patients, BPI has a high reliability ranging from 0.82 to 0.95 and high sensitivity to change among patients with arthritis (based on Wilks' lambda [$F(4,194) = 4.84, P = 0.001$]²². Participants also completed questionnaires pre and post 6 mo of treatment to assess muscle complaints using the Short-Form McGill Pain Questionnaire (SF-MPQ), which quantifies present pain intensity using both visual analogue and categorical scales²³. The SF-MPQ is one of the most commonly used research tools in the measure of pain with a reliability ranging from 0.83 and 0.84²².

Statistical Analyses

Differences in baseline characteristics between placebo and ATORVA groups were assessed with a one-way analysis of variance (ANOVA) with significance set $p < 0.05$. Data are reported as mean $\pm$ standard deviation (SD). Bivariate correlations were run to test for significant relationships between wellbeing, depression, and pain before and after 6mo of treatment vs. placebo. Repeated measures analysis of covariance (ANCOVA) tested between-group differences in the change of pain measures at 6 mo from baseline with sex and drug assignment as a fixed factor and baseline pain, age, and psychological health measures (i.e., PGWB, BDI) as covariates. Logistic regression tested the relationship between pain (severity or interference) as a binary outcome variable and depression or wellbeing as the independent predictor. Binary variables were created by coding patients as meeting the study definition of SAMS described above (study overview) or no SAMS. Furthermore, to capture any incremental changes in pain from baseline, but that did not meet the study definition of SAMS, binary variables were created by coding patients as having “any pain” (i.e., any changes in pain after 6 mo from baseline > 1.0 of a possible 10 on the BPI scale) or “no pain”. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 22.0 program for Windows (SPSS Inc, Chicago, IL).

Results

The total sample for this analysis ($n=83$) included healthy men ($n=38$) and women ($n=45$) who were, on average, middle aged, overweight, with optimal blood-lipoproteins and blood pressure (Table 1)^{24–26}. On average, participants had relatively low levels of depression (mean BDI: 4.4 ± 4.5) and high levels of psychological wellbeing (mean PGWB: 88.6 ± 15.9). Among the total sample, one patient was prescribed an anti-depressant and/or anti-anxiety medication (i.e., clozapine). At baseline, there were no between-group differences in overall wellbeing (PGWB), affective sub-groups of wellbeing, depression (BDI), or pain measures (SF-MPQ and BPI) (Table 2; $ps > 0.05$).

Baseline wellbeing (PGWB) correlated with baseline pain severity (BPI; $r = -0.290$, $p < 0.01$) and several activity and affective subcomponents including, enjoyment, walking ability, and general activity ($ps < 0.03$). Of the six affective sub-groups of wellbeing, general health correlated with baseline pain severity ($r = -0.593$, $p = 0.000$) and interference ($r = -0.380$, $p = 0.001$), while vitality correlated with baseline pain severity ($r = -0.288$, $p = 0.009$) and trended towards correlating with interference ($r = -1.94$, $p = 0.085$). Baseline depression correlated with baseline pain (SF-MPQ; $r = 0.313$, $p = 0.020$), but not interference ($p = 0.414$).

Overall wellbeing was not correlated with pain at 6mo among the entire sample ($p = 0.432$), however, baseline general health correlated with pain severity and interference at 6mo among the entire sample ($r = -0.384$, $p = 0.000$ and $r = -0.349$, $p = 0.001$, respectively). Baseline depression was not correlated with pain at 6mo among the entire sample or by group ($ps > 0.432$).

Both groups experienced an increase in pain after 6mo (placebo: 1.0 ± 0.2 to 1.3 ± 0.3 ; ATORVA: 1.0 ± 0.2 to 1.8 ± 0.3 , $p < 0.05$ for time effect), however, there were no differences between groups ($p = 0.270$, time $\times$ group interaction). Neither baseline depression, wellbeing,

or general health were significant covariates associated with pain or pain interference among the entire sample or by group (Figure 2; $p>0.698$ for group $\times$ time effect). Even when applying logistic regression analyses in order to capture a low threshold of pain as a dichotomous variable (i.e., pain vs. no pain), baseline psychological health indicators (i.e., depression; BDI and psychological wellbeing; PGWB) were not significant predictors of change in pain after 6 mo irrespective of group (Figure 3, $p=0.301$). Similarly, baseline depression and wellbeing were not significant predictors of documented SAMS (SAMS vs. no SAMS) in a logistic regression model ($p=0.297$).

Discussion

To the best of our knowledge, the present study is the first to examine the influence of baseline wellbeing and depression on self-reported muscle pain after initiation statin therapy. Poor baseline psychological health has been implicated in the onset and/or exacerbation of other health conditions such as hypertension²⁷, metabolic syndrome²⁸, CVD²⁹, mild cognitive impairment³⁰, and general pain³¹. However, in the present study, baseline wellbeing and depression were not significant predictors of pain change after 6 mo of ATORVA and do not appear to be associated with SAMS in otherwise healthy adults.

Psychosocial Health and Pain

The prevalence of pain as a symptom of diagnosed depression has been shown to be as high as ~60%³², with severity of depression positively associated with intensity of pain³³. Beneficial improvements in psychological wellbeing after cognitive behavioral therapy are associated with reduced pain sensitivity and severity³⁴. Previous research has focused on the physiological mechanisms underlying SAMS³⁵; consequently, the biopsychosocial influence of statin-associated muscle pain have been overlooked. By contrast, other similar muscle-related syndromes, such as fibromyalgia, are more recognized on the biopsychogenic continuum and are often treated successfully with the use of antidepressants³⁶.

There is preliminary evidence that serotonergic pathways could be implicated in SAMS. In an observational study of 7,924 patients with hyperlipidemia receiving high-dosage statin therapy, patients treated with antidepressants had a 50% reduction in SAMS and patients with a history of fibromyalgia-like symptoms were three times more likely to experience muscle pain on statins³⁷. There are genetic links to support these findings. Variants in the genes that encode for serotonin receptors *HTR3B* (rs2276307) and *HTR7* (rs1935349) are significantly correlated with myalgia scores in statin-treated patients³⁸. Thus, there is a rationale to infer that statin-induced myalgia may be mediated by depression or other psychological pathways (i.e., anxiety, stress); however, the present study does not provide evidence to support these associations.

SAMS

Because pain is a subjective experience, true SAMS is difficult to distinguish from muscle pain of other origins. Observational studies have reported the prevalence of muscle-associated side effects in statin users to be as high as 60%⁵. However, the present study, and other randomized-clinical placebo trials have found the incidence of SAMS to be much

lower (i.e., ~10%)^{39,40}. This discordance is most likely due to clinical trials employing a more stringent assessment of myalgia with study definitions and the use of a placebo arm to establish a causal relationship (i.e., muscle symptoms on statin re-challenge and no muscle symptoms on placebo)¹⁴.

It is possible that self-reports of *non-specific* muscle symptoms (i.e., did not meet the study definition of myalgia) were not captured in the STOMP trial⁹. However, the present study utilized a low threshold for self-report muscle complaints in a logistic regression model (i.e., any changes in pain after 6 mo from baseline >1.0 on the BPI scale) and found no changes in pain severity, pain intensity, or pain interference that were influenced by baseline psychological health (Figure 3). Furthermore, among the individuals within the present sub-study that met the study definition for myalgia (n=7), there were no differences in baseline depression scores (myalgia: 5.14±3.5 vs. no myalgia: 4.33±4.4; p=0.663) or psychological wellbeing (myalgia: 88±5.5 vs. no myalgia: 88.7±15.9; p=0.903). This is reassuring for statin prescribing clinicians who treat patients with comorbid depression and/or low psychological wellbeing as baseline psychological health indicators do not appear to mediate changes in muscle pain during statin treatment, even in patients with documented, SAMS in a placebo-controlled setting.

Limitations

The present study consists of a post hoc analysis of the larger STOMP trial and thus was not originally powered to examine baseline psychological wellbeing and/or depression on SAMS. However, with 40 participants on atorvastatin and a power of 0.80, we were powered to detect a difference of 1.04 at an alpha of 0.05, suggesting that negative findings were not due to type II statistical error. A major strength of the present study is that we examined the effect of a single, maximum daily dose of atorvastatin (80mg) for 6 mo versus placebo, thus significantly reducing variability in the statin-associated muscle complaint response. Prior studies have assessed statins of various doses and types, which may contribute to the heterogeneity in the published literature regarding the influence of statins on muscle complaints.

It is also noteworthy to mention that the present population had relatively high levels of psychological wellbeing and low levels of depression and this characteristic could explain the lack of association between psychological health indicators and self-reported pain. On average, the study population was classified as “minimally depressed” (mean BDI; 4.4±4.5). Future studies may consider examining self-reports of muscle complaints before and after statin treatment in a more clinically depressed population.

Clinical Implications

Statins are the most widely prescribed drugs in the US and the world^{3,41}. Application of the new American College of Cardiology/American Heart Association guidelines on the management of blood cholesterol would increase the number of US adults receiving or eligible for statin therapy from 43.2 million to 56 million, suggesting that the number of statin users will only continue to increase⁴¹. High rates of statin discontinuation due to muscle complaints (30–62%) underscore the need for researchers to better understand

individual factors underlying such reports⁵⁻⁷. The clinical consequences of suboptimal statin adherence or discontinuation of a prescribed statin are clinically meaningful⁷. Chowdhury et al. observed a 15% increase in CVD related events and a 45% increase in all-cause mortality in statin-using patients taking <80% of their prescribed statin therapy versus patients with higher adherence⁴². Thus, the development of a screening tool to better characterize and screen for patients who may be at risk for SAMS is imperative. Presently, suspected risk factors associated with SAMS are: high statin dose, lower body mass index, advanced age, female sex, heavy drinking, multisystemic diseases, and heavy exercise⁴³. To date, no studies have examined the influence of psychological health parameters on muscle pain reports after statin initiation. The present study provides preliminary data to refute any influence of psychological health on statin-associated muscle pain among healthy adults and focuses future research efforts considerably.

Conclusion

To conclude, baseline psychological health indicators did not appear to predict or influence the onset of muscle pain during 6 mo of high-dose statin therapy among a population of healthy adults with generally good wellbeing and low levels of depression at baseline. The relationship between mental health and muscle pain during statin therapy remains to be tested in a more clinically depressed population.

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Figure 1.
Study Protocol

Figure 2.
Pain Interference Before and After 6 months of Treatment Between Groups

Figure 3.
The Relationship Between Baseline Depression and Pain Interference after 6 Months of Treatment Between Groups.

Table 1

Baseline participant characteristics (mean±SD) between groups.

Variable	ATORVA (n=40)	Placebo (n=43)
Men/Women (%)	44/56	43/57
Age (years)	52 ± 13	54 ± 11
BMI (kg/m ²)	27.0 ± 4.5	26.7 ± 4.5
SBP (mmHg)	117 ± 12	115 ± 11
DBP (mmHg)	75 ± 9	73 ± 8
CK (U/L)	136 ± 113	113 ± 74
Total C (mg/dL)	207 ± 38	205 ± 37
LDL-C (mg/dL)	125 ± 35	123 ± 31
HDL-C (mg/dL)	60 ± 18	61 ± 15
Triglycerides (mg/dL)	111 ± 57	101 ± 44
Vitamin D (mg/dL)	33 ± 10	34 ± 13

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CK, creatine kinase; Total C, total cholesterol; LDL-C, low density lipoprotein; HDL-C, high density lipoprotein

Table 2

Baseline psychological health and pain characteristics (mean $\pm$ SD) between groups.

Variable	ATORVA (n=40)	Placebo (n=43)
Depression (BDI)	4.8 $\pm$ 3.5	4.0 $\pm$ 5.5
Wellbeing (PGWB)	88.3 $\pm$ 11.7	88.9 $\pm$ 19.1
Anxiety	19.8 $\pm$ 3.9	20.2 $\pm$ 3.8
Depressed mood	13.9 $\pm$ 1.5	13.5 $\pm$ 2.3
Positive well-being	14.9 $\pm$ 2.7	14.9 $\pm$ 3.2
Self-control	13.5 $\pm$ 1.8	13.9 $\pm$ 1.3
General health	12.2 $\pm$ 2.2	12.6 $\pm$ 1.9
Vitality	14.8 $\pm$ 2.7	15.5 $\pm$ 3.3
Pain severity (BPI)	0.27 $\pm$ 0.7	0.30 $\pm$ 0.7

BDI, Beck Depression Inventory; PGWB, Psychological General Well Being Index; BPI, Brief Pain Inventory