Published in final edited form as:
J Pain. 2011 November ; 12(11 Suppl): T102–T107. doi:10.1016/j.jpain.2011.08.009.

Summary of Findings from the OPPERA Baseline Case-Control Study: Implications and Future Directions

Roger B. Fillingim[1], **Gary D. Slade**[2,3], **Luda Diatchenko**[3,4,5], **Ronald Dubner**[6], **Joel D. Greenspan**[6], **Charles Knott**[7], **Richard Ohrbach**[8], and **William Maixner**[3,4,9]

[1]University of Florida, College of Dentistry, and North Florida/South Georgia Veterans Health System

[2]Department of Dental Ecology and Department of Epidemiology, University of North Carolina at Chapel Hill

[3]Center for Neurosensory Disorders, University of North Carolina at Chapel Hill

[4]Department of Endodontics, University of North Carolina at Chapel Hill

[5]Carolina Center for Genome Sciences at Chapel Hill, Chapel Hill, NC

[6]Department of Neural and Pain Sciences, University of Maryland Dental School

[7]Battelle Memorial Institute, Centers for Public Health Research and Evaluation

[8]Department of Oral Diagnostic Sciences, University at Buffalo

[9]Department of Pharmacology, University of North Carolina at Chapel Hill Chapel Hill, NC

The articles in this Compendium present first findings from the baseline case-control study of the OPPERA Program, a series of studies designed to identify risk factors for onset and persistence of painful Temporomandibular Disorders (TMD). This first series of manuscripts represents precursors to the ultimate goal of the OPPERA Program study, which is to build and then test a multivariable model designed to identify causal determinants of new onset TMD, as well as its chronicity. Embedded in OPPERA's baseline phase was a case-control study of chronic TMD, which collected extensive phenotypic and genotypic data from individuals with examiner-classified TMD arthralgia, myalgia, or both ("TMD cases") and people who were found not to have TMD when examined ("controls"). The heuristic model guiding the OPPERA study hypothesizes that development and clinical manifestation of TMD is driven by two global intermediate phenotypes, psychological distress and pain amplification, which in turn are influenced by both genetic factors and environmental exposures.[6] To address the model's hypotheses, phenotypic data were collected across

Please address all correspondence to: Roger B. Fillingim, Ph.D., University of Florida College of Dentistry, 1329 SW 16th Street, Room 5180, PO Box 103628, Gainesville, FL 32610-3628, Phone: (352) 273-5963, Fax: (352) 273-5985, rfilling@ufl.edu.

Disclosures
This work was supported by NIH grant U01DE017018. This material was also supported with by the North Florida/South Georgia Veterans Health System, Gainesville, FL. The OPPERA program also acknowledges resources specifically provided for this project by the respective host universities: University at Buffalo, University of Florida, University of Maryland-Baltimore, and University of North Carolina-Chapel Hill. Roger Fillingim and Gary Slade are consultants and equity stock holders, and William Maixner and Luda Diatchenko are cofounders and equity stock holders in Algynomics, Inc., a company providing research services in personalized pain medication and diagnostics. Richard Ohrbach, Joel Greenspan, Charles Knott, and Ronald Dubner declare that they have no conflicts of interest.

multiple domains, including socio-demographic, clinical, psychosocial, pain sensitivity, and autonomic function. Genetic data were also obtained in order to identify potential biological pathways underlying these intermediate phenotypes and thereby contributing causally to the development of TMD. After an overview, which provides the background and conceptual foundation for OPPERA, each of the subsequent articles reports associations between a particular phenotypic domain and TMD while the final article presents genetic associations with TMD. Rather than attempting a comprehensive analysis of this rich and complex dataset, the purpose of this first series of publications is to present the OPPERA data collection methods and to provide descriptive findings from this baseline phase. Future manuscripts will directly address the primary and secondary hypotheses of the OPPERA program.

Consistent with the epidemiological approach to case-control studies, this series of papers reports odds ratios as measures of the degree of association between putative risk factors and TMD.[10] For the numerous risk factors measured as continuous variables, such as psychological scales, standardized odds ratios were computed, representing the change in odds of TMD associated with an increase of one standard deviation of the continuous variable. The term “risk factor” is used broadly to represent variables (both etiologic events and characteristics) present prior to onset of TMD as well as those that occur during or after onset to exacerbate the symptoms of TMD. The variables of interest range from external causes of tissue damage to psychological and physiological processes affecting pain perception. Also included are commonly-occurring genetic variants that regulate biological pathways influencing those processes. Thus, across all manuscripts, the term “risk factor” conveys association and is not intended to imply causal influence or even temporal sequence. Below, we briefly summarize and integrate the major findings from each article and discuss future plans to elucidate factors underlying the development of TMD within the OPPERA Program.

Maixner, et al: Overview of the OPPERA Study

The initial article provides a brief historical overview of research exploring the epidemiology and risk factors for TMD, and discusses the development of the OPPERA conceptual model, providing additional definition of important constructs.[6] Based primarily on cross-sectional designs, previous investigators had identified potential risk factors for TMD, including: demographic (e.g. gender and age) and clinical (e.g. presence of other pain conditions) factors; pain amplification in the form of enhanced responses to experimentally-induced painful stimuli; and psychosocial factors, such as affective distress, somatic awareness, and psychosocial stress. The more recently developed and burgeoning literature regarding genetic influences on pain in general, and specifically on TMD, provides strong support for a genetic contribution to development of TMD. The aims and structure of the OPPERA Program are then presented. In addition to providing a useful conceptual foundation for the OPPERA Program, this overview article informs readers of the complexity of this project and acknowledges the invaluable support of both our Data Coordinating Center (Battelle Memorial Institute) and the National Institute of Dental and Craniofacial Research (NIDCR).

Slade, et al: OPPERA Methods, Recruitment, and Socio-demographic Findings

Slade et al. [11] present a thorough description of study designs for the OPPERA prospective cohort study, which is ongoing, and the baseline case-control study of 185 TMD cases and 1,633 controls, ages 18–44 years, which is the focus of this Compendium. Study methodology is also provided in detail, including: recruitment methods, inclusion/exclusion

and case-classification criteria, data collection procedures, training and calibration of clinical examiners, and methods for longitudinal follow-up of participants. The assumptions underlying sample size justification, the approach to data management and quality assurance, and the data analytic methods employed across all phenotypic domains in the baseline case-control study are also described.

One goal in selecting four study sites was to create demographic diversity in the cohort of people recruited for the OPPERA project. Another goal of recruitment was to select a community-based cohort of volunteers, both for cases and controls. The findings suggested that both goals were achieved. There was marked socio-demographic diversity between sites while within sites, the characteristics of OPPERA participants were generally comparable with population Census data from counties including and surrounding the study site. More than two thirds of TMD cases had first developed the condition at least three years prior to enrollment, though one quarter had never sought health care for their pain, and only 38% had received treatment for TMD from a health care professional within the preceding six months. The latter finding illustrates that the group of TMD cases comprised both patients receiving care and people with pain that was not currently managed with visits to a health care professional.

Greater age, female gender, and white racial/ethnic group were all associated with increased odds of TMD. Greater odds of TMD were modestly associated with higher educational attainment, though not with other markers of socioeconomic status. The four-fold greater odds of TMD in females relative to males and the pattern of age- and gender- associations were strikingly similar to benchmark data from the US National Health Interview Survey. Some of these findings confirm previous epidemiologic results, for example, gender differences in TMD prevalence have been well-documented.[5] However, limited and conflicting evidence exists regarding the association of age, ethnic/racial group and socioeconomic status with TMD. The higher frequency of TMD observed in non-Hispanic-Whites than in other racial/ethnic groups and the lack of a socio-economic gradient is in marked contrast to the pattern of disparities seen for most other health conditions [12].

Ohrbach, et al: OPPERA Clinical Findings and Pain Symptoms

The manuscript by Ohrbach et al[8] presents clinical findings from the OPPERA case-control study, and describes methods for collecting phenotypic variables across multiple clinical domains, including: history of trauma, parafunctional behaviors, other pain or functional disorders, clinical signs and symptoms, anthropometric measures, and medical history. Several of these measures fall within the “environmental contribution” depicted in the OPPERA heuristic model, while some others represent sub-clinical signs and symptoms of TMD, or represent comorbid pain conditions that can occur with TMD. The findings verify, as expected, that cases not only reported greater facial pain severity and pain-related interference than controls, but also greater limitations in jaw function, more frequent joint noises (clicking, crepitus), increased pain with function, and enhanced palpation sensitivity compared to controls. Numerous case-control differences were also observed in putative risk factors, with cases reporting greater occurrence of jaw injury, increased numbers of parafunctional behaviors, and higher frequency of other pain conditions, including headache, back pain, and irritable bowel syndrome. For several of those putative risk factors, odds ratios of five or more were observed, signifying strong associations with TMD. An important consideration noted by Ohrbach and colleagues [8] relates to the lack of information regarding temporal sequencing of many potential risk factors and TMD onset, such that causal relationships between experience of potential “risk factors” and the development of TMD cannot be inferred. Indeed, a given variable, such as parafunctional behaviors, could represent an antecedent causal contributor, an exacerbating factor in patients with existing

TMD, or simply a consequence of experiencing TMD-related pain. OPPERA's prospective cohort study will be able to address these issues, because it will establish whether or not potential risk factors are present prior to onset of TMD. However, the current case-control study cannot address the question for the many potential risk factors that might vary throughout a person's lifetime. Given that many of the clinical variables are directly related to the signs or symptoms used to classify TMD, these issues related to causal inferences are particularly salient in this manuscript; however, this issue applies across all phenotypic domains and will be further discussed below.

Fillingim, et al: Psychosocial Findings from the OPPERA Study

Fillingim et al[3] present associations between TMD and psychosocial measures representing the intermediate phenotype of "psychological distress" as specified in the OPPERA heuristic model. Based on published literature, self-report instruments were administered assessing psychosocial phenotypes across several conceptual domains, including: personality/global psychological adjustment, mood/affect, psychosocial stress, somatic awareness, and pain coping and catastrophizing. Findings indicated case-control differences across all domains, with the strongest associations observed for somatic awareness, where standardized odds ratios exceeded 2.0. Moderately strong associations were observed for measures of affective distress and catastrophizing. Principal component analysis (PCA) was performed in the control sample to identify latent constructs across the multiple psychological measures, which yielded a model with the following four components: 1) Stress and Negative Affectivity, 2) Global Psychological Symptoms, 3) Passive Pain Coping (including catastrophizing), and 4) Active Pain Coping. These PCA findings indicate that multiple underlying psychological constructs are present and are important to consider as potential risk factors for TMD. While previous studies have examined psychological function in patients with TMD [1,2,9], the OPPERA assessment battery represents perhaps the most comprehensive evaluation to date of psychological phenotypes in people with TMD. Of particular note is the finding that somatic awareness showed the strongest association with TMD case status, rather than more traditional psychological risk factors such as mood or perceived stress. As noted for the clinical data, psychosocial phenotypes such as increased psychological distress, somatic awareness, and maladaptive pain coping, may represent consequences and/or exacerbating factors rather than etiologic factors contributing to onset of TMD, a possibility to be directly evaluated in the prospective study.

Greenspan, et al: Quantitative Sensory Testing Findings from the OPPERA Study

Greenspan et al.[4] present the findings regarding experimental pain sensitivity, which aims to operationalize the intermediate phenotype of "pain amplification" as specified in the OPPERA heuristic model and further defined in the Overview paper.[6] The manuscript describes in detail the OPPERA quantitative sensory testing (QST) procedures, which were used to characterize multiple aspects of experimental pain sensitivity, including: sensitivity to pressure, mechanical cutaneous, and heat pain stimuli, as well as more dynamic measures of temporal summation of heat and mechanical pain. Statistically significant case-control differences emerged for most measures of pain sensitivity, with the largest differences observed for pressure pain thresholds and cutaneous mechanical pain threshold. Standardized odds ratios of 2.0 or more, reflecting strong associations, were observed even when the measurements were made on the shoulders, arm and hand, well away from the temporomandibular joints, muscles and related tissues. Using data from the controls, PCA identified five latent constructs in the QST data: (1) heat pain ratings, (2) heat pain aftersensations and tolerance, (3) mechanical cutaneous pain sensitivity, (4) pressure pain

thresholds, and (5) heat pain temporal summation. Overall, these findings indicate that TMD cases show statistically significantly greater extracranial pain sensitivity across multiple QST domains, and that measures of pressure pain sensitivity are particularly strongly associated with odds of TMD. The prospective study will allow determination of whether this state of pain amplification represents a premorbid risk factor for development of new onset TMD.

Maixner, et al: Autonomic Findings from the OPPERA Study

In the next article in the series, Maixner and colleagues [7] present novel findings regarding autonomic function in TMD cases and controls. In the OPPERA heuristic model, autonomic function is characterized as a putative mechanism contributing to pain amplification. As Maixner and colleagues note, several lines of evidence implicate disruptions of autonomically-mediated pain inhibitory pathways in chronic pain conditions. Given its comprehensive autonomic phenotyping, the OPPERA Program has the opportunity to determine for the first time whether autonomic dysregulation represents a potentially causal risk indicator for TMD.

The OPPERA Program performed extensive autonomic phenotyping, including the following measures: blood pressure, heart rate, heart rate variability (HRV), and indirect measures of baroreflex sensitivity, all of which were assessed at rest and in response to a physical and a psychological stressor. Several autonomic measures differed between cases and controls, such that greater odds of TMD was associated with increased heart rate, reduced heart rate variability, and possibly reduced baroreflex sensitivity across all experimental procedures. Odds ratios of 1.2 – 1.4 were found for the statistically significant associations, indicating generally modest effects of greater heart rate and lower parasympathetic tone on odds of TMD. PCA of the autonomic measures from the control sample identified five components: 1) blood pressure (across all experimental tasks), 2) HRV during psychological stress (i.e. the Stroop test), 3) heart rate (across all experimental tasks), 4) resting HRV, and 5) HRV during physical stress (i.e. orthostatic challenge). Taken together, the findings suggest a pattern of autonomic dysregulation characterized by increased cardiosympathetic and reduced cardioparasympathetic tone among TMD cases compared to controls. Though the magnitude of most associations is modest, indices reflecting autonomic function represent a set of biological processes that may contribute unique variance to the prediction of TMD.

Smith, et al: Genetic Findings from the OPPERA Study

The final article in this Compendium examines genetic associations with TMD.[13] In the OPPERA heuristic model, commonly-occurring genetic variants are depicted as an “upstream” set of etiologic influences because they regulate enzymes, neurotransmitters, receptors and structural proteins that are essential for the biological processes occurring in chronic pain. For the OPPERA Program, DNA samples extracted from whole blood were genotyped for 3295 single nucleotide polymorphisms (SNPs) representing 358 genes involved in biological systems relevant to pain perception. This study represents the first genetic association study of TMD to investigate an extensive panel of pain related candidate genes.

Data quality procedures and statistical analysis methods are described in detail. Given the modest number of TMD cases available in the OPPERA cohort, this genetic association study supplemented the OPPERA sample with 182 additional TMD cases from another project at the University of North Carolina (the UNC cohort). A two-tier analytic approach was adopted, in which a small subset of genes investigated in previous studies of pain was

hypothesized *a priori* as high priority and subjected to a less stringent correction for determining statistical significance. The remaining genes were considered Tier 2, or exploratory genes, with an increased error correction threshold.

For Tier 1 genes, eight SNPs were noteworthy because the p-value for their association with TMD diverged from the p-value distribution expected under the null hypothesis. They comprised 3 SNPs tagging adrenergic receptor genes (1 SNP of ADRA2C, 2 ADRA1D SNPs), a SNP of the catechol-O-methyltransferase gene (COMT), a delta opioid receptor (OPRD1) gene SNP, two SNPs in the region of the interleukin 10 (IL10) gene, and a SNP of the of the GRIN2A ionotropic N-methyl-D-aspartate (NMDA) receptor 2A gene. For most of these SNPs, minor allele frequency was at least 20%, and odds ratios approximated either 1.5, signifying greater odds of TMD associated with the minor allele, or 0.6 signifying a similar magnitude of a protective association. (Reverse coding for the major allele would produce corresponding odds ratios of 1/1.5 = 0.7 and 1/0.6 = 1.7.) Some larger odds ratios were observed for SNPs with lower allele frequency.

For Tier 2 genes, nine SNPs across six genes were associated with TMD case status with p-values exceeding what would be expected due to chance. Three of the SNPs were in the region of the glucocorticoid gene (NR3C1), one was a SNP of the serotonin 2A receptor gene (HTR2A), two SNPs were on the calcium/calmodulin-dependent protein kinase 4 gene (CAMK4), one was in the muscarinic cholinergic receptor 2 (CHRM2) gene, one SNP was in the interferon-related developmental regulator 1 (IFRD1) gene, and one SNP was in the G protein-coupled receptor kinase 5 (GRK5) gene. While the authors acknowledge the need for replication of the results, and the findings strongly suggest that multiple genetic loci and biological pathways contribute to risk for TMD.

Conclusions and Future Directions

Taken together, the findings across this set of manuscripts demonstrate that these TMD cases differ from controls across multiple phenotypic domains. Specifically, odds of TMD were associated with socio-demographic factors, clinical variables, psychological functioning, pain sensitivity, and autonomic responses. Also, several novel genetic associations with TMD were identified, providing clues to the biological pathways that may contribute to TMD pathophysiology.

Not surprisingly, the strongest associations with TMD were observed for measures related to the manifest features of TMD: bodily tenderness (e.g. pressure pain thresholds) and salience of symptoms (e.g. somatic awareness). Odds ratios were smaller, signifying weaker associations, for measures of phenotypes depicted as more distal mechanisms in the OPPERA heuristic model, including mood, autonomic function, impaired temporal regulation of pain and genetic variants. While this observation is subject to several of the caveats considered below, the findings provide preliminary support for the OPPERA heuristic model. Further, the broad range of phenotypic domains that distinguish cases from controls reflects the complex and multidimensional nature of TMD etiopathogenesis, which we have referred to as a "web of causation."[6,8]

As noted above, the term "risk factors" connotes etiologic events and characteristics, yet for many risk factors of interest, this case-control study evaluates association, not causation. Indeed, for some of the phenotypic variables it is plausible that the measured characteristic represents both a cause and a consequence of TMD. For example, Ohrbach et al[8] discuss the evidence showing that parafunctional behaviors such as clenching can not only contribute to onset of TMD, but can also occur as an adaptive response to it. Similar, bi-directional associations can easily be envisaged for many measures of psychological distress and pain

amplification. The cross-sectional findings presented in this Compendium do not address this issue and the phenotypic findings presented must be interpreted only as associations. In principle, odds ratios for associations with these “bi-directional” phenotypes will be greater than the causal odds ratio that would be observed if only the etiological component of the association could be dissected. This principle probably accounts for several of the very strong associations observed for several clinical measures, and it may contribute to strong associations seen for measures such as somatic awareness. The prospective study of the OPPERA Project is designed to determine the temporal sequence in which phenotypic risk factors and onset of TMD unfold, and ultimately to identify true causal determinants of TMD. Notable exceptions to these limitations are genotypes and other immutable characteristics: age, gender, and race/ethnicity.

Another interpretive consideration for these results is that the association of risk factors with TMD was examined in univariate fashion in these analyses, controlling only for study site, age, gender and race. It is likely that the magnitude of these associations, and possibly even their direction, will change in multivariate analyses that consider combined contributions of more than one putative risk factor to TMD. For example, in the analysis of psychological variables, both perceived stress and negative affect were associated with increased odds of TMD; however, it is conceivable that after statistical adjustment for perceived stress, negative affect may no longer show a significant association with TMD. Furthermore, most of these analyses evaluate odds of TMD only as a linear function of the measured phenotype, yet non-linear relationships are likely for some measures, and might be informative about processes underlying the association. The OPPERA program will be investigating such relationships in the near future as case accrual and data collection ends.

There are several additional future directions that the OPPERA investigators plan to pursue to exploit this very rich compilation of phenotypic and genotypic data that promises to illuminate the pathophysiological processes that contribute to TMD. For example, we have not yet explored the benefits of incorporating measures across phenotypic domains (e.g. psychological and pain sensitivity measures) into multivariable analyses to increase our ability to disentangle combined etiologic influences and to distinguish cases from controls. It seems plausible that individuals with high risk phenotypes in both psychological distress and pain amplification domains would show greater odds of TMD than those people with a risk phenotype in only one of these domains. Analyses to empirically examine this hypothesis will be conducted in the future. Also, the OPPERA heuristic model proposes that the association of genetic factors with TMD risk is mediated by the intermediate phenotypes of pain amplification and psychological distress, which interact with environmental exposures to influence TMD risk. Therefore, OPPERA investigators plan to conduct association studies to directly identify genetic factors contributing to pain amplification and psychological distress. Of course, these planned analyses represent precursors to the ultimate goal of the OPPERA Program, which is to build and then test a multivariable model designed to identify true causal determinants of new onset TMD, as well as its persistence. The results of these first case-control studies support our conceptual model, which increases our confidence that these future efforts will be successful.

Acknowledgments

The authors would like to thank the OPPERA research staff for their invaluable contributions to this work. In addition, we express our gratitude to the participants who have devoted time and effort in support of this research.

Reference List

1. Carlson CR. Psychological considerations for chronic orofacial pain. Oral Maxillofac Surg Clin North Am. 2008; 20:185–95. [PubMed: 18343324]

2. Eli I. Psychosocial factors in the etiology, diagnosis and management of temporomandibular disorders. Alpha Omegan. 2003; 96:20–3. [PubMed: 12955778]

3. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Dubner R, Bair E, Baraian C, Slade GD, Maixner W. Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011; XX:XXX–XXX.

4. Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, Knott C, Mulkey F, Rothwell R, Maixner W. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. J Pain. 2011; XX:XXX–XXX.

5. LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Critical Reviews in Oral Biology & Medicine. 1997; 8:291–305. [PubMed: 9260045]

6. Maixner W, Diatchenko L, Dubner R, Fillingim RB, Greenspan JD, Ohrbach R, Weir B, Slade GD. Orofacial pain prospective evaluation and risk assessment study - the OPPERA study. Journal of Pain J Pain. 2011; XX:XXX–XXX.

7. Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V, Knott C, Slade GD, Ohrbach R, Fillingim RB. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011; XX:XXX–XXX.

8. Ohrbach R, Fillingim RB, Mulkey F, Gonzalez Y, Gordon S, Gremillion H, Feng Lim P, Rieiro-Dasilva M, Greenspan JD, Knott C, Maixner W, Slade GD. Clinical Findings and Pain Symptoms as Potential Risk Factors for Chronic TMD: Descriptive Data and Empirically Identified Domains from the OPPERA Case-Control Study. J Pain. 2011; XX:XXX–XXX.

9. Rollman GB, Gillespie JM. The role of psychosocial factors in temporomandibular disorders. Current Reviews of Pain. 2000; 4:71–81.

10. Schlesselman, JJ. Case control studies: design, conduct, analysis. New York: Oxford University Press; 1982.

11. Slade GD, Bair E, By K, Mulkey F, Baraian C, Rothwell R, Reynolds M, Miller V, Gonzalez Y, Gordon S, Ribeiro-Dasilva M, Feng Lim P, Greenspan JD, Dubner R, Fillingim RB, Diatchenko L, Maixner W, Dampier D, Knott C, Ohrbach R. Study methods, recruitment, socio-demographic findings and demographic generalizability in the OPPERA study. J Pain. 2011; XX:XXX–XXX.

12. Smedley, BD.; Stith, AY.; Nelson, ARE. Unequal treatment. Washington, D.C: The National Academies Press; 2003.

13. Smith SB, Maixner D, Greenspan JD, Dubner R, Fillingim RB, Ohrbach R, Knott C, Slade G, Bair E, Gibson DG, Zaykin D, Weir B, Maixner W, Diatchenko L. Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. J Pain. 2011; XX:XXX–XXX.