A suggested 5 year research agenda for temporomandibular disorders

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INTRODUCTION

I would like to begin this presentation with a quote attributed to a famous writer Mr. C. F. Kettering. He said

"Research is a word that scares a lot of people. It needn’t. It is rather simple. Essentially, it is nothing but a state of mind—a friendly, welcoming attitude toward change. Going out to look for change, instead of waiting for it to come. Research, for practical men, is an effort to do things better and not to be caught asleep at the switch. The research state of mind can apply to anything. Personal affairs or any kind of business, big or little. It is the problem-solving mind as contrasted to the let-well-enough-alone mind; it is the ‘tomorrow mind’ instead of the ‘yesterday mind’.”

Given that everyone agrees with Mr. Kettering’s attitude, then research becomes an essential skill we need to impart to every student. In fact, an education consisting of an accumulation of known facts is indeed a poor education, since many “facts” of today will not be “facts” tomorrow. Since many of us and all of our students will be practicing in the twenty-first century, it is incumbent on all teachers to educate their students to be competent practitioners in this future world. To achieve such a goal, it is obvious that we cannot teach them “today’s facts” alone: even teaching principles, or concepts, or techniques are not enough, since these change also. Treatment and diagnostic procedures we think are good today, certainly will not be valid forever. The diseases we treat today may
not even exist in the future and new diseases will come along to replace them. The challenge in education today is to produce an inquiring mind. This is only done by exposing the student to research at all levels. Dental educators must provide courses which teach students the following: a) the methodology of research; b) how and where to find pertinent information; c) how to evaluate the validity of research; and, d) how to apply research methodologies to the problem at hand.

I. A GOOD RESEARCH QUESTION

In order to perform good research it is essential to first understand what actually constitutes good research. Good research begins with the selection of a research question which in its final form must be stated as a null hypothesis. In choosing this question, the scientist should initially begin with a broadly focused question and then refine the question into one or more specific and narrowly focused questions that are contained within the broader question. Far too often the research question is not selected with enough care to its relevance. What I mean by this is that because research requires so much time and often expensive resources, it is important to be sure the question you have selected to pursue passes the “So what?” or “Who cares?” test. Don’t waste time pursuing questions that once you have the answer, no one will care about it. Another way of examining the value of a question is to estimate the impact (number of people who will be effected by the answer) and the quality of the answer (will everyone accept the evidence you have or will they say the project was scientifically flawed?).

In addition to the relevance of the question, it is essential to consider the feasibility of the question as well. The feasibility of a research question is usually based on the quality of the actual research protocol being proposed as the method to answer the question than the question itself. To a grant reviewer, the feasibility of a research protocol is judged by how well the scientist describes in the protocol the following issues: a) what is already known about the topic (this is included in the literature review section); b) why are you, as principal investigator, likely to be able to conduct this project successfully; and c) are the design and measurements to be used likely to answer the question under consideration (this is in the material and methods section). Like relevance, the feasibility judgment of the protocol must pass the—“Would you give money for this project?”—test.

II. COMPONENT PARTS OF A RESEARCH PROTOCOL

After selecting a question it is essential for the researcher to begin writing a detailed research protocol. Table 1 contains a brief list of the essential information which is
needed in the materials and methods section of a research protocol. As can be seen in this table, the scientist must specify the Research Design of the protocol. There are numerous research designs which can be selected, and, to a large extent, the question being asked may determine the type of design which is appropriate. The two basic designs are observational studies which are also called descriptive or non-hypothetical studies. Examples of observational studies are cross-sectional studies (one time point measurement) and longitudinal studies (multiple time point measurement). The later can be either retrospective or prospective in direction. In general, observational studies can never answer a cause and effect question, it can only show association between variables. The other major type of study is an Experimental study which is also called an interventional or hypothetical based study. The research design in a experimental study should be further described as being randomized and controlled if such a design is incorporated. Control conditions are typically either placebo, waiting list, or comparison interventions. The only way to approach the answer to a cause and effect question is via an experiment which has random assignment, blindly and is controlled.

III. THE QUALITY OF A RESEARCH PROTOCOL

The quality of a research protocol is best assessed by judging how well the component parts are put together. In Table 2 are the elements needed to have a quality research protocol. A quality assessment of the protocol begins by estimating the validity of the proposed study. Validity involves both the internal validity (a.k.a. confidence in the results) and the external validity (a.k.a. real world application of the results). For example, a study specifies that it will gather data on an intended study sample or population. It should then be asked “how likely are the investigators going to be able to actually get the data they want from their intended sample?” Next it must be asked “if they can get the data, is their intended sample data generalizable to the target real world sample?” Similar questions should be asked about the planned measurements (variables): “are the measurements being made representative of the variable of interest,” and “do the variables selected actually represent the phenomena or disease of interest?”

A well designed study is one that has a plan to prevent the common research errors. Error prevention is done as a feature of research design, but occasionally errors occur anyway, and many times error correction can be done in the data analysis plan. The most common type of errors and the methods to reduce their effect are: Random error (increase sample size to minimize); Systematic error or bias (check the validity of all measurements and build in methods for removing bias by blinding of the examiners and replicating
the study at another experimental site). Examples of systematic error are sampling problems and measurement error.

IV. CAUSAL INFERENCE

The last item listed in Table 2 above is called “Causal inference strengthening strategies”. This aspect of the protocol is the most difficult to achieve. Basically it means that you have considered and dealt with alternate concepts which could explain the data.
The quintessential feature of a quality research protocol is how strongly the resulting data allows a cause and effect determination to be made. This is described as “Causal inference”, and the investigator must always remember that because two variables are correlated or associated, this does not prove a cause and effect relationship. The strength of the causal inference which can be made from an experiment is an inherent feature of the design and analysis plans of the study and is the essence of what defines research quality.

V. TMD SPECIFIC RESEARCH ISSUES

The primary signs and symptoms of TMD are pain and tenderness in the masticatory muscles and/or the temporomandibular joints, sometimes combined with joint sounds and limitations or disturbance of mandibular movement (e.g., jaw “locking”, restricted jaw opening, or chewing problems). Such signs and symptoms often occur in the context of etiologically distinct disorders, adding complexity to differential diagnosis. Some TMD problems appear to arise directly from degenerative or inflammatory changes within the TMJ. Others appear to reflect increased vulnerability to injury or disruptions of reparative processes following macro- or micro-trauma within the TMJ or masticatory muscles. Abnormalities in muscle function or structure also may contribute to the persistent muscle fatigue and soreness commonly reported. Behavioral factors also appear to contribute to the onset or exacerbation of symptoms for some patients with TMD.

In 1989, a group of scientists were gathered by the National Institute of Dental Research (NIDR) to put together a research plan for the 1990’s. This plan was published in 1990 and included multiple recommendations about research which was needed in the arena of TM joint function and trigeminal sensation. In 1994, an NIDR-sponsored meeting of scien-
tists was held which summarized available clinical and scientific information on the TMD and identified promising research directions. This International Workshop on the TMD and Related Pain Conditions was also published in book form in 1995. At this meeting participants recommended a major expansion of research to clarify the etiology and pathogenesis of these conditions. Topics included in this paper include recommendations for research into the pathogenesis and etiology of TM disorders. The result of this publication was that many areas of research were suggested as promising areas. In this article we have listed 9 specific areas. Where the authors have expertise and experience we have supplemented these 9 recommended areas with additional suggestions.

VI. NINE SUGGESTED RESEARCH TOPICS

1. Identify biologic markers:

At the present time there are no widely accepted biologic markers of disease for the most common Temporomandibular disorders. For definition purposes, a biologic marker is considered to be a molecular, cellular or clinical feature which when identified is characteristic of the disease entity and only exists in the presence of disease. It would be useful to identify biologic markers of disease which would allow both the identification and staging of the severity of the disease. For example, the presence of RA factor in the blood is considered a reasonably good biologic marker for the presence of Rheumatoid Arthritis.

Although they may be difficult to identify, it would be extremely useful to identify and validate any molecular and cellular changes which might serve to be a biologic marker of the three main conditions which affect the jaw system, namely myofascial pain, internal derangement or localized arthritis of the TM joint. Towards this goal, research which elucidates the molecular mechanisms involved in the synthesis, maintenance, and degradation of these tissues in disease states is needed. Such research could focus on the molecular mechanisms that cells use to synthesize, maintain, and degrade the extracellular matrix.

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and tissues and could include genetic regulation and the effects of hormones, mediators, pharmacologic agents, mechanical roads, aging, and developmental changes. Research could determine the molecular and cellular composition of each tissue (e.g., expression of genes, level of proteins) in normal and dysfunctional tissues.

2. Describe the response of the masticatory system to injury:

Characterize neural plasticity at molecular, cellular, and physiological level in response to injuries involving the TMJ and masticatory muscles (including the introduction of artificial materials and devices). Such studies should characterize plasticity at peripheral and segmental levels in ascending pathways and descending pathways. Studies should look at the processes involved in sensorimotor integration. These studies should include consideration of various neurotransmitters, neuromodulators, and transcellular and intracellular messengers involved in nociception and plasticity.

3. Further describe the neural mechanisms of pain:

Define central nociceptive pathways activated in response to injury of the TMJ, masticatory muscles, or other orofacial tissues and characterize modulatory processes influencing such activation. Such studies need to examine the various neurotransmitters, neuromodulators, and transcellular and intracellular messengers involved in nociception.

4. Investigate the efficacy of various therapeutic interventions:

a) Conduct randomized controlled clinical trials to assess the effectiveness of avoidance exercise therapy for clicking patients, especially in the young patient with more recent onset. The exercise–avoidance approach was advocated to help reduce TMJ clicking\(^3\). However, there are no data on the efficacy of the exercise–avoidance approach compared to a no treatment approach. Avoidance of a persistent click has been reported to be ineffective in eliminating the jaw joint clicking phenomena\(^9\). In the young patient with more recent onset TMJ click problems, some exercises reportedly helped eliminate the click\(^5\). The degree to which spontaneous remission occurred in the latter report is not known. This avoidance approach seems empirically logical and may be a reasonable treatment alternative for a patient with a persistent TMJ click\(^6\). Results of research suggest that most clicking patterns do not change and few develop into or lead to serious TM joint locking or degenerative joint disease\(^7\).

b) Conduct randomized controlled clinical trials to assess the long-term effectiveness of repositioning splints and reconstructing (surgically, orthodontic, or prosthetic) for clicking patients. Data suggest that the stabilization splint has poor efficacy for management of TMJ clicking\(^8,9\). For repositioning splints, the short-term (one year or less) data suggest that these splints can clearly modify, if not eliminate, some TMJ clicking problems\(^10,11\).
The long term data, however, are less convincing, with approximately one-third or fewer of these patients experiencing a permanent change in their clicking pattern\textsuperscript{12,13}. Because the cost of reconstructing (either surgically, orthodontic, or prosthetic) a permanently repositioned occlusion is substantial and irreversible, this approach does not seem warranted except in rare cases. There are several problems with the design of the studies upon which conclusions regarding the efficacy of repositioning for TMJ clicking are based\textsuperscript{14,15}. Few of the studies used random assignment and none were “double blind” evaluation studies. In addition, there are no good methods of measuring clicking across a prolonged period of time in the natural environment. All prior data are based on patient self-report or a laboratory-based measurement of clicking. Laboratory-based assessments are useful, but how frequent the problem occurs in the day-to-day routine is more relevant than how loud a click is in the laboratory. The development of portable long-term TMJ noise measuring technology would be beneficial to future studies of TMJ clicking. Last, the criteria for selecting cases which “require” permanent repositioning are not clear and need to be refined and tested.

c) Conduct randomized controlled clinical trials to assess the effectiveness of sodium hyaluronate for clicking patients. Joint surface lubrication using a sodium hyaluronate (HA) is the final physical medicine technique to be considered. Data from other joints (knee) where HA infusion has been used suggest that a high molecular weight hyaluronate has the potential to be a conservative, safe, efficacious, and essentially hazard-free adjunctive “lubricating” agent to reduce joint friction and promote healing of intracapsular disorders. In one well-controlled study, injections of HA were moderately efficacious for management of painful symptoms associated with TMJ clicking, but the clicking did not disappear\textsuperscript{16}. This is the only paper with data based on a random assignment controlled multi-site clinical trial. The HA infusion procedure is limited because HA is not yet approved by the Food and Drug Administration (FDA) in the U.S.A. for intra-articular use in humans.

d) Conduct randomized controlled clinical trials to assess the effectiveness of manual manipulation, arthrocentesis or arthroscopic lavage or lysis for closed lock patients. Since the mid 1970’s, the patient with acute onset loss of TMJ motion has been managed with methods which directly invade or manipulate the joint. For a 10-year period (from approximately 1978 to 1988), open TMJ disc repositioning surgery was widely performed. This procedure was described as a method for treating closed lock problems. Since the advent of arthroscopic surgery\textsuperscript{17} in 1986, the closed locking problem has been managed with this less invasive and more effective method\textsuperscript{18}. Whether manual manipulation, arth-
rocentesis or the actual arthroscopic lavage or lysis is the most important way to manage these cases has not been established. Moreover, arthrographic imaging showed a normal disc position following manipulation in only a few cases.

e) Conduct randomized controlled clinical trials to assess the effectiveness of repositioning splints after successful manual manipulation for closed lock patients. Many authors who reported success also described a post manipulation protocol involving the insertion of a mandibular repositioning splint. They assumed that the clicking and looking would recur if no appliance were used\(^{19,20}\). Whether the appliance is necessary after manipulation has never been addressed by a RCT. Actually, the frequent use of such a protocol might suggest that the results of manipulation are short-term except one non-randomly assigned and non-controlled report. Conduct randomized controlled clinical trials to assess the pure arthroscopic effectiveness, and compare them with the conventional physical therapy. Indications for TMJ arthroscopy were continuous, painful, closed locking and a failure of the manual reduction technique to resolve the problem. No RCTs have been conducted for arthroscopy of the TMJ compared to the conventional physical therapy, and for that reason, it is clear that additional series of well-designed comparative diagnostic methodology studies are still needed\(^{21}\). It is therefore, impossible to distinguish the surgical effect from the post-operative physical therapy program or the steroid injections used in most cases. In addition, some cases of closed lock will resolve fully without invasive therapy\(^{22,23}\), and others progress to a rapid degeneration of the articular surfaces.

f) Conduct randomized controlled clinical trials to assess the effectiveness of a jaw rest/soft diet/non-steroidal anti-inflammatory drug (NSAID) regime for TMJ pain patients. Clinical case reports and therapeutic logic generally support the claim that the rest/soft-diet/NSAID approach is helpful for acute trauma induced joint pain. However, there are few well designed clinical outcome research studies that have been conducted which specifically evaluate the efficacy of individual physical medicine techniques to relieve TMJ pain beyond a brief therapeutic period.

g) Conduct randomized controlled clinical trials to assess the effectiveness of stabilization splints for TMJ pain patients. Even if stabilization splint was induced to alter joint function and reduce articular surface loading, chronic TMJ pain appears to respond only weakly to that\(^{24,25}\). Better scientific research is needed to evaluate its efficacy for this condition.

h) Conduct randomized controlled clinical trials to assess the effectiveness of the relative treatment approaches for TMJ pain patients. TMJ pain rarely occurs as an isolated problem and secondary myogenous symptoms are usually present. If joint pain appears to
be caused by repeated parafunctional behavior (e.g., bruxism), an occlusal stabilization appliance may be added to the treatment regime. Whether or not the occlusal appliance can alter loading in the TMJ has not been proven, but clinically it does seem to alter parafunctional behaviors. The rest/soft diet/NSAID method in combination with an occlusal appliance approach has not been compared to other available approaches using RCT testing. Clearly, comparative studies are needed to determine the relative effectiveness of treatment approaches (i.e., physical-medicine versus pharmacologic versus surgical therapy).

i) Conduct randomized controlled clinical trials to assess the effectiveness of topically applied anti-inflammatory modalities or transcutaneously induced anti-inflammatory medications for TMJ pain patients.

No RCT tests have evaluated the efficacy of topically applied anti-inflammatory modalities or transcutaneously induced anti-inflammatory medications. There are many case-based reports which are generally positive. However, one study compared these modalities with a control condition in the chronic back and neck pain patient and reported no clear benefits. Conduct randomized controlled patient trials to assess the effectiveness of stretching and range of motion exercises for TMJ pain patients. Non-pharmacologic physical medicine procedures have not been reported to reverse or stop any polyarthritic joint disease process. However, the same physical medicine procedures described for localized TMJ pain management are commonly prescribed to provide symptomatic treatment for polyarthritic origin TMJ pain and its secondary myogenous symptoms. In addition, stretching and range of motion exercises are commonly prescribed to maintain or increase joint mobility. When intra-articular osseous changes exist patients often avoid movement of the involved joint. Although movement avoidance is appropriate for acute joint pain, joint mobilization is generally considered important in the management of chronic joint pain. Unfortunately, no data from RCT are available in which the efficacy of these procedures was tested in the polyarthritic disease afflicted TMJ.

j) Conduct randomized controlled clinical trials to determine the efficacy of various treatment modalities for muscle pain patients, especially the rest/soft-diet/NSAID treatment program versus a no-treatment approach for acute muscle pain problems.

The rest/soft-diet/NSAID treatment program is commonly prescribed to provide symptomatic treatment for acute muscle pain problems. However, no RCTs have been performed to compare the effectiveness of the rest/soft-diet/NSAID treatment program with a no-treatment approach for acute onset myalgia and myositis in the masticatory muscles. The ultrasound/ice pack/heat pack/exercise/trigger point injections/acupuncture/TENS/...
muscle stimulation/cold laser treatment programs versus a no-treatment approach for chronic muscle pain problem are needed. When the muscle pain disorder is recalcitrant to treatment and therefore considered chronic, other methods are traditionally prescribed such as topically applied pain relief and inflammation reducing modalities. The proposed mechanism by which these modalities provide pain relief and inflammation reduction is via an increase in regional arterial perfusion. However, these treatment modalities have not been fully tested for efficacy. The most reasonable data on physical medicine modalities for treatment of chronic jaw muscle pain concerns acupuncture. However, if a credible pseudo-acupuncture treatment were tested in an RCT these findings might weaken. Additional testing of acupuncture versus a control condition and other myalgic management methods seems warranted. Comparative studies of various physical medicine methods of treating musculoskeletal pain in other anatomic areas have not consistently rated one method better than another. Further, when traditional physical medicine procedures were tested against behavioral medicine methods (e.g., biofeedback or other stress management methods), there is similar efficacy suggesting that a strong behavioral component is present in most physical medicine methods or that there is a strong physical component in behavioral methods. At present, none of these modalities have been shown to be superior to a credible pseudo-therapy control condition.

k) Conduct randomized clinical trials to determine the efficacy of stabilization splints for muscle pain patients, especially for the problems of spontaneous onset chronic myofascial pain. Occlusal splints have been utilized for many years to treat this condition under the assumption that masticatory muscle parafunction was contributing to the pain production. Several studies have shown that the stabilization splint is a moderately powerful treatment for modifying parafunctional activities in the jaw and decreasing myalgia based symptoms \(^{24,30}\). In the muscle pain patient without a strong parafunctional origin to his/her symptoms, however, it appears that splints are comparable to both acupuncture treatment and most other behavioral therapies \(^{31}\). Further, if a credible pseudo-therapy is used in a clinical trial on pain of musculoskeletal origin, stabilization splints were not shown to be superior to the pseudo-therapy \(^{32}\). When either stabilization splints or behavioral therapy for TMD are compared to a no-treatment or wait-list program, these treatments are almost always reported by patients to be strongly helpful, while the no-treatment program has a weak effect. It appears that at least for the problems of spontaneous onset chronic myofascial pain, the mechanism of the stabilization appliance is not known and might best be conceptualized as a behavior modifying device.

l) Conduct randomized controlled clinical trials to determine the efficacy of various
treatment modalities for trismus and splinting patients.

Trismus and splinting of the masticatory muscles result in a decreased range of voluntary jaw opening. Limited mandibular movements may also occur for a number of non-muscular reasons. For this discussion, however, decreased range of mandibular movement is assumed to be a protective reflex induced during opening in which jaw opening muscles are inhibited and jaw closing muscles are excited. A common physical medicine approach utilized for patients with complaints of trismus is ice and/or vapocoolant spray application to the skin over the painful muscle followed by stretching of the involved muscles. Advocates of vapocoolant spray and stretch procedures claim that stretching helps alleviate chronic myofascial pain and dysfunction by desensitizing the “trigger point” in the muscle. Although the mechanism is not known, the clinical effectiveness of this procedure has been accepted due to clinical success. Trismus is usually a symptom secondary to regional pain. Treatment of trismus without appropriate management of the underlying pathology is not likely to be efficacious. Other approaches utilized for the treatment of trismus involve high voltage galvanic stimulation as well as ultrasound of the involved muscles. These treatments reduce pain and inflammation and, if followed by stretching procedures, have been reported to alleviate the trismus response. In general, for physical medicine, procedures must be repeated frequently to be effective in increasing mandibular range of motion. When post-treatment relief is transient, greater attention must be paid to etiologic factors. RCT data are needed to identify the most efficacious physical medicine approach for the management of trismus.

m) Conduct randomized clinical trials to determine the efficacy of stabilization splint for trismus patients. Anecdotally, it is widely known that stabilization splints are used with great effect to treat trismus, probably because they alter parafunctional behaviors. Unfortunately, there is no specific research on the effect of splints on trismus.

n) Conduct randomized clinical trials to determine the efficacy of physical medicine procedures for the diagnosis of dyskinesia. The literature does not support the effectiveness of any physical medicine procedures in the management of involuntary motor disorders except as a purely palliative measure. Exercise methods involving movement feedback can help mild masticatory muscle incoordination problems if they are learned behaviors. Additional research needs to be performed comparing the various treatment methods for masticatory muscle pain, trismus and movement incoordination problems. Differentiate dyskinesia with neurologic disorders (e.g., focal mandibular dystonia or facial tics). The goal is to relieve the myalgic pain as the patient’s motor control improves. Theoretically, this improvement results from increased awareness of his/her muscles. As this
occurs, the patient is better able to recognize when the muscles are contracting and when they are relaxed\textsuperscript{29}. The above motor control problem should not be confused with true involuntary orofacial dyskinesia (e.g., focal mandibular dystonia or facial tics). These latter conditions are neurologic disorders and should be evaluated and treated as such\textsuperscript{26}.

5. **Investigate the mechanism of chronic muscle pain:**

Despite the high prevalence of chronic muscle pain, there is still a lack of understanding of the underlying mechanisms which cause and sustain the pain. A potentially fruitful area to explore in the quest for a better understanding of this disorder is the study of contraction induced muscle hemodynamics. The human mandibular motor system appears to be an excellent experimental model for studying chronic muscle pain. Changes in motor activation and intramuscular perfusion should be explored using a power spectral signal analysis of surface EMG and direct and indirect methods of monitoring blood flow. Methods such as Magnetic Resonance Spectroscopy, Xenon 133 and NIR spectroscopy should be employed to study the hemodynamics of a muscle both in vivo and in vitro and in vitro in animal tissues\textsuperscript{34}. To induce these changes in the muscle, an experimental task needs to be employed, such as maximum isometric contractions (MVC) held for a set period of time with and without vasoconstrictive stimuli (e.g. cold pressor and pharmacologic vasodilators). Because of the nature of disease, a good research design would be a "case-control" based experiments. The specific research question to be explored is whether a localized intramuscular hypoxia is an important determinate in the production and maintenance of chronic masticatory muscle pain in humans.

6. **Describe and characterize the TM disk-joint surface interface in health and disease:**

a) Determine the role of the jaw movement and function in the maintenance of the molecular, cellular, and morphological integrity of the TMJ: In more specific, the following research are recommended. Develop the objective arthroscopic criteria and test against an asymptomatic control group. Establishing the diagnostic utility of the intracapsular pathologies unique to TMD patients is one area of current research. For example, direct arthroscopic visualization of the joint’s inner structures has allowed more definitive descriptions of tissue-specific intracapsular pathology to be performed in vivo. The common pathologies described by this method are synovitis, chondromalacia, and adhesions. Unfortunately, the current criteria defining these pathologic entities are still highly subjective and, given the invasive nature of the arthroscopic procedure, the criteria have never been tested against an asymptomatic control group\textsuperscript{35,36}.

b) Examine the function of the disk and its lubricating fluids rather than the static
position of the disk: Once the general TM Disorder group and its subgroups have been defined using clinical examination methods, the next logical step would be to make more refined diagnoses of tissue-specific intra and extracapsular pathologies unique to TMD patients. In this regard, TM joint tissue imaging using magnetic resonance imaging (MRI), direct arthroscopic inspection of the joint tissue, and chemical analysis of aspirated joint fluids offers great promise for defining intracapsular pathologies.

Recent research shows that a reasonably large percentage of asymptomatic subjects have an abnormal TMJ disk position\(^{37-39}\). These data suggest that it may be more appropriate to examine the function of the disk and its lubricating fluids rather than the static position of the disk\(^{40}\). One method of assessing TM joint function is to directly examine the disk and other joint surfaces for local pathologic change using arthroscopy. Unfortunately, most of the published arthroscopic studies are descriptive reports of a series of cases and have no comparison or control data to validate the reported changes as truly pathologic. A second method for evaluating function is to assay the fluid in the TM joint for characteristic changes associated with clinical diseases.

c) Examine the lower joint cavity and compare with the upper joint cavity: At present, most studies have been conducted for only upper joint compartment examination, leaving the lower compartment unexplored. With recent advancements in the optical equipment of arthroscopy, it is now possible to explore the lower joint cavity. Kondoh and Westesson\(^{41}\) (1991) performed experimental lower joint arthroscopy in comparison with postmortem morphology. The relationship of the pathologies between upper and lower joint cavities has not been described, and supplemented data from other institutions is needed.

d) Test to see whether synovitis, chondromalacia, and adhesions between disk and articular surface are related to clinical symptoms or signs: Because arthroscopy is an invasive procedure, this diagnostic tool is not appropriate as a screening device for TMD. Its logical primary use will be to refine the existing clinically based TMD diagnosis with regard to the specific joint tissue abnormality and its severity. Exactly which cases need a refined diagnosis is not yet established, because, as mentioned above, the predictive values for TMJ arthroscopy are based on cadaver research. Although cadaver research is useful, the validity of those judgments can only be confirmed in vivo against an asymptomatic control group. Such a study will be difficult to perform for obvious reasons. Positive arthroscopic findings such as synovitis, chondromalacia (believed to be an early sign of degenerative change), and adhesions between disk and articular surface are the most promising pathologic entities which warrant study. These three entities, as
opposed to advanced osteoarthritis changes, are conditions which cannot be obtained with other diagnostic methods (i.e., radiographs) and therefore should be tested to see whether these findings are related to clinical symptoms or signs.

e) Define the significance of synovitis in relation to clinical signs: The presence of synovitis in the absence of clinical signs raises questions about both the validity of the synovitis rating criteria and pathologic significance of this finding. Future research on this topic needs to be performed with calibrated, blind-to-subject-status clinical and arthroscopic examiners. In addition, refined clinical pain rating scales (e.g., visual analog scale) and standard pressure application devices (e.g., pressure algometer) need to be employed to evaluate joint soreness. Finally, it should be noted that the current method of rating synovitis by arthroscopy is very subjective and therefore difficult to standardize.

f) Examine joint fluid content with both patients and controls and attempt additional correlations of clinical symptoms and arthroscopic observation: Joint fluid markers of disease may be useful because it is possible to assay this fluid in both patients and controls. Future research must attempt additional correlations of clinical symptoms, arthroscopic observation, and joint fluid content with a larger data set and a more refined clinical symptom analysis. Pure descriptive reports of pathologic findings in clinical cases without controls are no longer adequate to advance our diagnostic skills and help our patients.

7. Look for and prove the validity of clinical markers of TM disease:

The practicing clinician’s “gold standard” for TMD is patient self-report in combination with a validating clinical examination. This combination is necessary, because at present, TMDs have no reliable biologic or histopathologic markers, a substantial segment of the general population have one or more of the characteristic signs or minor symptoms, and the condition is more or less defined as being present only when it has a substantial impact on the patient’s life or well-being.

a) Decide the number of muscle and TMJ sites that need to exhibit tenderness and how severe the site tenderness must be in order to define the presence of TMD for clinical research purposes: No agreement exists on the number of muscle and TMJ sites that need to exhibit tenderness and how severe the site tenderness must be in order to define the presence of TMD for clinical research purposes.

b) Practice reliability studies of examination methods: One essential aspect of validity is the precision or reliability of an examination procedure. It is important to distinguish between two types of examiner reliability, one referring to the consistency of each individual to perform the same task over and again (i.e., intra-examiner reliability) and the other
indicating if the same consistency exists between individuals when making observations of
the same variable (i.e., inter-examiner reliability). An observer’s reliability reflects the
precision of the measurement but is not an indication of its accuracy (i.e., validity). In
other works agreement may exist, yet examiners may be wrong when compared to a gold
standard. In order to test for consistency or reliability, standardization of the examina-
tion protocol, as well as training and calibration of examiners, is needed to ensure that
each technical step of a selected procedure is performed according to recommended guide-
lines. Another prerequisite in any reliability study is that specific criteria be stated
regarding the interpretation of any clinical sign and symptom which requires a clinical
judgment. Reliability studies must also fulfill several other basic requirements 47). Unfor-
tunately, these requirements were rarely complied with in prior TMD examination studies
as pointed out by Dworkin et al. 48) in a previous review.

c) Calibrate examiners to consistently perform technical tasks related to muscle and
joint palpation: For research purposes, calibration procedures and set criteria for accept-
able examiner performance were suggested in the assessment of muscle and TMJ tender-
ness 49). Undoubtedly, training and calibration protocols for TMD examiners will need to
be extended and refined in the future. These protocols must involve the following: a
reproducibility study assessing consistency of other clinical examination methods during
repeated exams of both TMD patients and control subjects, as well as testing of
examiners’ performance over a period of time following their calibration.

d) Standardize muscle and joint tenderness examinations: There is a consensus that
muscle tenderness is an important clinical sign in myofascial pain and related
musculoskeletal disorders. Digital (i.e., fingertip) muscle palpation represents a potential
clinical test, with other clinical findings, which may help discriminate subtypes of TMD
patients in a selection process for clinical trials. However, with the exception of a few
studies and despite the fact that digital muscle palpation is widely used, very few opera-
tional guidelines are explicitly described to assist clinicians and researchers to systematize
and standardize the procedure in an attempt to enhance its reproducibility. Thus, the
validity of manual palpation as an assessment technique for TMD has not been fully estab-
lished 50). Palpation involves several steps, among which are the technical aspects of
which fingers are used, the amount of pressure applied, the site being palpated, and the
selection of a pain measurement tool (e.g., visual analog score, polychotomous rating scale,
or a dichotomous system). While various pressures have been arbitrarily selected by differ-
ent investigator teams, this decision should be supported by data showing the discrimina-
tive value of such pressure. Although there are no published studies reporting palpation
of the same muscle sites as described in the research diagnostic criteria, the cross-sectional study evaluated 16 of 20 sites used in the Research Diagnostic Criteria \(^{51}\). This finding suggests that females may have an elevated response to muscle palpation and that establishing optimal cut-off levels may require consideration of gender effect. Our report \(^{46}\) addressing the amount of pressure applied has suggested that the pressure currently selected by Fricton and Schiffman \(^{52}\) Dworkin et al. \(^{53}\) (respectively 1 and 2 pounds) may be too low for muscle tenderness assessment and associated with an unacceptable false negative rate. Undoubtedly, more research is needed to specify if whole muscle palpation presents an advantage over the palpation of selected, specific muscle sites. It is also unclear which method of grading severity (i.e., patient verbal report of tenderness using a dichotomous pain scale, a multiple validated pain word descriptor scale, or examiner assessment of patient reaction to palpation) is most reliable. All of these factors must be taken into consideration, since it may differently influence the precision and ultimate validity of muscle and joint pain detection methods. As more objective methods to detect and quantify subjective muscle and joint pain symptoms become available, a better definition of disease state will be developed. The digital (i.e., fingertip) pressure method remains the current gold standard, and any new methods (i.e., pressure algometry) must be compared to it to identify all of its advantages and possible shortcomings \(^{50}\). Clearly, results of the reliability studies on assessment of tenderness illustrate that research using this clinical parameter to diagnostically discriminate patients from non-patients must use a reproducible examination technique.

e) Standardize mandibular movement examinations: Because limited jaw opening is frequently seen in TMD patients, measurement of maximum pain-free, maximum unassisted, and maximum passive opening range of mandibular movement is an essential element of a clinical examination. The gold standard for evaluation of mandibular movement remains the use of the millimeter ruler \(^{46,54}\), a technique that has been shown to be highly reproducible within and between investigators \(^{49,53}\). This method, however, cannot be used to assess dynamic movement irregularities such as abnormal but non restricted pathways of movement. Whether dynamic movement assessment is important diagnostically has yet to be determined. Suggested alternative measures include electronic kinesiologic instruments, however, these instruments are unreliable in the lateral measures and demonstrate significant error in both vertical and lateral movement \(^{55–57}\), so these unreliable and invalid electronic measures should not be used to acquire information for diagnosis of TMDs.

f) Standardize temporomandibular joint sound examination: Joint sounds are a characteristic feature of many TMD patients, but the simple presence of these sounds does not
define the disease labeled “TMD,” as many people have joint sounds without any demonstrable illness. Therefore, the character, severity, and timing of the joint sound must be clinically assessed to determine if disease is present. A review indicated that a common clinical diagnostic procedure to detect TMJ sounds using light finger palpation of the TMJ during motion is moderately reproducible between examiners, and may not be adequately reliable for research purposes. It is also evident that further variation will result where there are differences in examination procedures, especially where the examiners are untrained and not calibrated. At present, no real attempt has been made to correlate the interexaminer variability to any specific factors that could account for variability of the joint sounds themselves. Other factors influencing joint sound evaluation include the speed and path of the jaw movement. An inherent inaccuracy of the examination to determine the timing of a dynamic measure such as TMJ sounds is the fact that the use of a millimeter ruler requires a static position of the mandible. Finally, the best method for assessing the severity of the TMJ sounds has not been agreed upon.

g) Validate questionnaires and standardize the use of these procedures: The literature is reviewed with respect to the utility and validity of the different questionnaire and examination procedures that have been used to assess Temporomandibular Disorder (TMD) patients. The presented view is that many of these procedures have not been validated, that there is a lack of standardization in the use of the procedures themselves, and that an ideal method of classifying this broad group of patients into better defined subgroups has not yet been developed. More standardized and better defined research by trained and calibrated researchers is needed worldwide to elucidate these subgroups so that a better and widely agreed upon research classification system can be developed for widespread use.

h) Test a set of research diagnostic criteria (RDC) for TMD and improve some shortcomings: a National Institute of Dental Research conference was sponsored to help develop a set of research diagnostic criteria (RDC) for TMD. These new guidelines were published in late 1992 and will undoubtedly improve upon the shortcomings of the prior systems. The new RDC are separated into a clinical examination-based axis and a chronic pain disability and psychological-based questionnaire axis. At present it would be considered as the best TMD research diagnostic criteria, but it remains to be seen whether they will be the definitive TMD research diagnostic criteria. This hesitation is based on the fact that any clinical examination-based diagnostic specification system for TMD must be based on data which show that the individual component examination items are the correct parameters to use. Before assuming that the new RDC are the ultimate criteria,
it would be more logical to test and compare several of the published palpation systems which have been used in prior research. Another problem with the proposed RDC is the adoption of terminology to describe internal derangements which require actual dynamic visualization of the disk to confirm that disk displacement occurs with or without reduction. However, disk imaging is not required to use the terminology. It might be best to use a less specific anatomic term (e.g., disk-condyle dysfunction or incoordination with or without intracapsular restriction) to describe the clinical findings until confirmatory imaging is performed. One of the major advantages in the new criteria is rules regarding how to deal with a patient who has symptoms which would qualify him or her in several of the TMD diagnostic subgroups. Unfortunately, this system does not yet provide a way of scoring the relative strength of each diagnostic subgroup when multiple attributions are made. Finally, a second axis of diagnosis in the domain of pain related disabilities and psychological disorders is proposed and described. As with the clinical signs and symptom-based axis, this proposed system will need critical assessment and validation from comparative studies with other psychosocial assessment instruments which claim utility as psychological-based axes of diagnosis. While these newly proposed research definitions are an improvement over prior definitions, they have not yet been tested for precision, validity, or utility. Researchers attempting to use any of the available diagnostic systems must first establish the precision, validity, and utility of the system in a more rigorous fashion than has been done in the past.

i) Address the issue of symptom overlap and create a system which allows multiple subgroup attributions as well as score-specific symptom levels when multiple signs and symptoms exist so that the relative strength of each subgroup assignment can be assessed. As a starting point, any research diagnostic categorization system must at least deal with the four cardinal clinical features of TMD (i.e., masticatory muscle pain, TMJ pain, TMJ noises, and restriction of mouth opening). For TMJ and muscle tenderness assessment, the exact location, method, and pressure parameters must be specified. For TMJ noise and mandibular movement assessment, the verbal instructions, sequence of examination, and method of measurement must also be specified. These specifications must be based on data, reproducible, and validated as being discriminatory items. Only when such criteria are available will individual symptom and sign scores be combinable for categorizing patients into various TMD subcategories. Although there is not universal agreement on a classification schema for the TMDs, many U.S. clinical scientists have begun using a set of research diagnostic criteria (RDC) that categorize clinical TMD conditions within three broad clusters (i.e., muscle diagnoses; disc displacement; and joint disorders consist-
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8. Describe the natural course of the major TM disorders:

Conduct studies to clarify relationships between fibromyalgia and temporomandibular myofascial pain, to determine the natural course of disc displacement and osteoarthritis, or to clarify the biological effects of TMJ disc displacement on surrounding tissues.

9. Develop a theory explaining the gender bias of TM disorders:

A preponderance of females have been noted in most studies of patients seeking care for the TMDs. Initially, this was thought to reflect gender-related differences in health care seeking behaviors or differences in tolerance for pain and other physical symptoms \(^{62}\). However, several recent epidemiological studies indicate overall associations between female gender and vulnerability to joint and muscle disorders \(^{63}\). Such findings suggest the need to evaluate how hormonal or other gender-related factors influence the development of disorders, such as the TMDs, involving joints and muscles.

FINAL COMMENTS

The above suggestions that more attention be paid to selecting the question and implementing careful research methods can not be emphasized strongly enough. The subsequent lists of TMD research topics given in this article are provided only as a guide for novice researchers looking for questions of importance. At best this information will help researchers establish the future agenda of investigations needed to advance the discipline. Finally we wish to remind all individuals treating patients or performing research in this field that the typical problems seen in TMD patients are not usually disabling or extremely long-lasting. Even when TMD symptoms are prolonged for more than 6 months, they are not disabling and, in most patients do not interfere substantially with the patient’s work life or social life (except eating). There may, however, be iatrogenic damage from irreversible therapy. For this reason, conservative treatments with reasonable efficacy should be selected and advocated. Second, a conceptual framework for organizing and understanding the available treatments is helpful. In this regard, the most common method of treatment for TMD problems includes a combination of techniques derived from a physical medicine model (e.g., physical therapy and physical medicine procedures applied at home or in the office including dental occlusal appliances) and a behavioral medicine model (e.g., counseling, biofeedback, stress management, and relaxation training). These two models are generally considered reversible treatments with a low morbidity and a very
high efficacy. Because some of the conditions afflicting the TMJ produce a clear and substantial interference in function, two additional minimally invasive models of care are also commonly used: the pharmacologic model (e.g., non-steroidal anti-inflammatory medications, antidepressant medications, antispasmodic medications, and steroid injections), and the closed joint surgical manipulation model (e.g. arthrocentesis and arthroscopy). Both of these latter models have greater potential risks, but if selected for the right patient and used in the right situation, they should have low morbidity and good efficacy. Finally, in all areas of medicine, it is assumed that if a correct and specific diagnosis is made, appropriate and logical treatment will follow. Unfortunately, diagnosis is difficult and the choice of therapy is not simple. Treatments are selected based on numerous factors including cost, risk-benefit ratio, prior experience, degree of invasiveness, the patient’s confidence in the care provider, and the care provider’s judgment regarding which treatment would best help the patient. The latter can not be determined without a substantial increase in our research knowledge base.

REFERENCES

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これからの5年間に予測される顎関節に関連する障害（TMD）についての研究課題

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抄録 本論文では、まず歯科医学教育において、研究方法、適切な情報収集、研究の評価および身近な問題に対する研究方法の適応について教えることの重要性を述べた。ついてで研究のためには1. 研究上の疑問、2. 研究計画における構成要素、3. 研究計画の質および4. 因果関係の推定が必要であることを概説した。そして顎関節に関連する障害（TMD と以下略す）における研究の焦点について触れた上で、これからの5年間に予測される TMD に関する研究課題として、1. 正常と異常の識別法、2. 外傷に対する咀嚼系の反応、3. 痛みの神経機構、4. 種々の治療法の有効性、5. 慢性筋痛の機序、6. 関節円板と関節との接触面における生理と病態、7. TMD における生物学的マーカーの追求と有効性、8. 主要な TMD の自然経過、9. TMD における性的偏りの解明を挙げた。特にそれら9課題については文献的検討を加えつつ、それぞれの問題点について考察した。

キーワード TMD, 研究課題, 研究計画

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