Medication in temporomandibular disorders and bruxism

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Nog finns det mål och mening i vår färd -
men det är vägen, som är mödan värd.

Karin Boye 1900-1949

To Christian, Fredrik and Johan with love

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ABSTRACT

The aim of this thesis was to explore aspects of pharmaceutical intervention in temporomandibular disorders (TMDs) and bruxism. Sleep bruxism is a movement disorder that signals disturbed sleep and constitutes a significant health problem due to TMDs, headache and tooth wear. In **Study I,** medication was reviewed in patients referred for specialist treatment for TMDs. Female patients with myofascial pain used significantly more psychoactive medication, including antidepressants, tranquilizers, sedatives and hypnotics, compared with matched controls. These findings support other research demonstrating an overrepresentation of the diagnoses depression, anxiety, stress and sleep problems among TMD patients. **Study II** compared the effect of oral glucosamine sulfate on osteoarthritis in the temporomandibular joints with that of placebo. Glucosamine sulfate appeared to improve signs and symptoms over time, but it was not significantly superior to placebo. In **Study III,** the dopamine agonist, pramipexole, was investigated in severe sleep bruxism confirmed by polysomnographic/electromyographic monitoring. The severity of sleep bruxism was not reduced compared with control conditions, indicating that the involvement of the dopamine system in bruxism is less likely. In **Study IV,** the effects of botulinum toxin injections in the masticatory muscles, compared with placebo injections, were evaluated in subjects with cerebral palsy and bruxism. No significant differences between active and control injections in terms of subjective or objective oral functions could be observed at group level. **In conclusion**, the results were negative with respect to the evaluated pharmacologic remedies for TMDs and bruxism. There is a relative lack of controlled studies in this area. Considering the pronounced negative impact on quality of life that has been reported for these conditions, it should be an important task continuously to evaluate putative pharmacologic therapies in TMDs and bruxism.

Keywords: temporomandibular disorders, sleep bruxism, glucosamine sulfate, pramipexole, dopamine agonist, botulinum toxin, cerebral palsy

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SAMMANFATTNING PÅ SVENSKA

Smärta och funktionsstörningar i tuggmuskulaturen, käkleder och angränsande strukturer, temporomandibular disorders (TMDs), liksom tandpressning och tandgnissling (bruxism) är vanligt och kan orsaka stora problem och onödigt lidande för den drabbade. De bakomliggande orsakerna till TMDs och bruxism är inte helt klarlagda och varierar troligtvis mellan olika subgrupper. Bland de behandlingar som kan lindra finns läkemedel. **Syftet** med avhandlingen var att undersöka olika aspekter på läkemedelsbehandlingar vid TMDs och bruxism. Sömn-bruxism kan vara tecken på sömnstörning och ett uttalat hälsoproblem som kan leda till TMDs, huvudvärk men också tandslitage. I **Studie I** registrerades regelbunden användning av läkemedel hos TMD patienter som var remitterade till en bettfysiologisk specialistklinik. Kvinnliga patienter med tuggmuskelsmärta använde signifikant mer antidepressiv, lugnande och sömnmedicinering vid jämförelse med matchade kontrollpatienter från en allmäntandvårdsklinik. Resultatet är i överensstämmelse med tidigare undersökningar vilka visat på en överrepresentation av depression ångest, oro, stress och sömnproblem hos patienter med TMDs. **Studie II** jämförde behandlingseffekten av glukosaminsulfat i tablettform vid smärtsam käkledsartros med placebotabletter. Symtomen minskade i båda grupperna men inte tillräckligt mycket i den aktiva gruppen för att kunna visa att glukosamin var signifikant bättre än placebo. I **Studie III** undersöktes dopaminagonisten pramipexol hos patienter med uttalad sömn-bruxism med hjälp av polysomnografi och elektromyografi. Läkemedlet pramipexol används för att stimulera dopaminreceptorerna i hjärnan. Sömn-bruxismen minskade inte efter medicinering med pramipexol jämfört med kontrollbetingelser. Detta indikerar att dopaminsystemet troligtvis inte är involverat vid bruxism. I **Studie IV** jämfördes effekten av botulinumtoxin-injektioner i tuggmuskulaturen med placebo-injektioner hos personer med cerebral pares och bruxism. Ingen signifikant skillnad mellan botulinumtoxin-gruppen och placebo-gruppen i objektiva eller subjektiva mätvärden kunde registreras. **Sammanfattningsvis** visade de undersökta läkemedlen inte på någon effekt, varken vid TMDs eller bruxism. Det finns få läkemedelsstudier som berör det aktuella området. Eftersom båda tillstånden kan påverka livskvalitén negativt är det angeläget att fortsätta utvärdera farmakologisk behandling i kontrollerade studier, både för TMDs och bruxism.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Johansson Cahlin B, Samuelsson N, Dahlström L.
Utilization of pharmaceuticals among patients with temporomandibular disorders: a controlled study.
Acta Odontol Scand. 2006;64(3):187-92.

II. Cahlin BJ, Dahlström L.
No effect of glucosamine sulfate on osteoarthritis in the temporomandibular joint – a randomized, controlled, short-term study.
Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(6):760-6.

III. Cahlin BJ, Hedner J, Dahlström L.
A randomized, open-label, cross-over study of the dopamine agonist, pramipexole, in patients with sleep bruxism.
Submitted to the J Sleep Res.

IV. Cahlin BJ, Lindberg C, Dahlström L.
Cerebral palsy and bruxism: effects of botulinum toxin injections – a randomized, controlled trial.
In manuscript

CONTENT

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
ATC	Anatomical therapeutic chemical classification
BTX-A	Botulinum toxin-A
CAHI	Central apnea-hypopnea index
CI	Confidence interval
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
CP	Cerebral palsy
ECG	Electrocardiogram/electrocardiography
EEG	Electroencephalogram/electroencephalography
EMG	Electromyogram/electromyography
EOG	Electrooculogram/electrooculography
ESS	Epworth sleepiness scale
FOSQ	Functional outcomes of sleep questionnaire
GABA	Gamma aminobutyric acid
GOHAI	General oral health assessment index
IASP	The International Association for the Study of Pain
ICSD	International classification of sleep disorders
IRLSS	International restless legs syndrome scale

ISI	Insomnia severity index
KSS	Karolinska sleepiness scale
Mean sat	Mean saturation
MOS	Medical outcomes study sleep scale
MVC	Maximum voluntary contraction
N	Newton
N1	NREM stage 1
N2	NREM stage 2
N3	NREM stage 3
NAW	Number of awakenings
NNT	Number needed to treat
NREM	Non-rapid eye movement, non-REM
NS	Non significant
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
ODI	Oxygen desaturation index
OPPERA	Orofacial pain: prospective evaluation and risk assessment
OSA	Obstructive sleep apnea
PLM	Periodic limb movements
PPX	Pramipexole
PROM	Patient-reported outcome measures

PSG	Polysomnogram/polysomnography
PSQI	Pittsburgh sleep quality index
RDC	Research diagnostic criteria
RDI	Respiratory disturbance index
REM	Rapid eye movement
RLS/WED	Restless legs syndrome/Willis-Ekbom disease
RMMA	Rhythmic masticatory muscle activity
SB	Sleep bruxism
SD	Standard deviation
SF-36	Short form health survey 36
TAI	Total arousal index
TMD	Temporomandibular disorder
TMI	Temporomandibular index
TMJ	Temporomandibular joint
TST	Total sleep time
VAS	Visual analog scale
VRS	Verbal rating scale
WHO	World Health Organization

1 INTRODUCTION

Temporomandibular disorders (TMDs) are heterogeneous conditions characterized primarily by pain in the masticatory system but also by mandibular dysfunction and temporomandibular joint (TMJ) sounds (1, 2). Persistent orofacial pain is the overwhelming reason for seeking TMD treatment (1) and can result in impaired general health and a devastating impact on the quality of life of the affected patients (3). For example, myofascial pain is associated with sleep disturbances (4, 5) and there is some support for the hypothesis that sleep disturbances aggravate chronic orofacial pain (6), but another study does not agree (7).

Sleep bruxism (SB), defined as clenching and grinding of the teeth (8), may lead to temporomandibular disorders, headache and tooth wear (9). SB is a sleep-related movement disorders and can be a sign of disturbed sleep (10).

Neither TMDs nor SB are new conditions and the Bible actually wrote about bruxism in association with stress, anxiety and depression. In the Gospel of Luke 13:28, it says "There shall be weeping and gnashing of teeth, when ye shall see Abraham, and Isaac, and Jacob, and all the prophets, in the kingdom of God, and yourselves cast forth without".

There is no single effective cure for TMDs, despite many evidence-based treatments such as stabilization splints, behavioral therapy, biofeedback, physiotherapy and TMJ surgery (11). To our knowledge, there is no better treatment for SB than protective stabilization splints. Factors that might be helpful in TMDs and bruxism include pharmacologic substances, but there is still a lack of evidence for many of the drugs used and side-effects are frequent (12).

1.1 Pain

1.1.1 Definition

The International Association for the Study of Pain's (IASP) widely used definition states that "pain is an unpleasant sensory and/or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (13). To summarize, pain is always subjective and linked to both emotional and psychological reactions, regardless of whether or not it is a tissue injury. Pain also produces multiple plastic changes in the CNS which involve the learning system and memory (14).

1.1.2 Gender differences in pain

There are differences between men and women in their responses to pain (15, 16) with a higher prevalence of TMDs, chronic tension-type headache, migraine and fibromyalgia, for example, among women in reproductive ages than for other age groups or men (17). Facts relating to the experience of pain severity for men and women are contradictory (18, 19). Biologic (sex hormones, endogenous opioid functions, different genotypes) and psychosocial causes (stress-exposure, pain coping) are factors influencing pain that are reported, with a higher sensitivity in women (17, 20). The response to pharmacologic treatment can also differ between men and women. The reason for this is still unclear, but there are probably gender related differences in the characteristics of pain (20).

1.1.3 TMDs

Description of the condition

TMDs describe a group of musculoskeletal conditions classified as being primarily of masticatory muscles origins, intra-capsular derangements of the TMJ components or degenerative changes in the bony components of the TMJ. The signs and symptoms associated with TMDs vary, but pain is usually the main complaint, originating from the temporal area and the cheek but also in the peri-auricular area. In addition to the presence of pain, TMDs are characterized by limitations in jaw movement and joint sounds from the TMJ during function (2).

TMDs can start as an acute condition, but some become chronic. A few patients have pain only occasionally, while in others it is intermittent. Another group have pain all the time. Mild conditions may debilitate over time, but more severe conditions tend to be chronic (21, 22). The genesis of chronic pain conditions is complex and comorbidity between TMDs and pain-related disorders from other parts of the body has been shown (23). Pain lasting for at least three months is classified as long term or chronic. TMDs are the most common chronic orofacial pain conditions of non-dental origin and occur with the same prevalence as other chronic pain problems such as headache and back pain conditions (2, 24).

Epidemiology

Overall, about 10%-12% of the population over 18 years of age suffer from TMDs (25). The conditions are most prevalent in women in their child-bearing years (20-40 years), with a decrease in distribution with age (26). In adults, twice as many women as men are affected (25, 27). TMDs are less common in childhood and there is no gender difference until adolescence (12-19 years),

when the prevalence in girls increases to 6% compared with 2.7% for boys (28, 29). For patients with a disc diagnosis, a peak has been identified around the age of 30 and, for those with inflammatory or degenerative joint diagnoses, the peak is over the age of 50 (30).

Etiology

TMDs are not always clearly understood and the etiology may vary in the different subgroups. Age and gender (*e.g.* younger age and female gender) are the most reliable risk factors for TMDs (2) and an underlying vulnerability to experience pain can exist in some individuals (28). Many theories have been tabled, rejected and debated when it comes to whether the putative risk factors represent causal influences on the risk of developing TMDs or actually are a consequence of TMDs (27). In chronic TMD patients, factors such as the sensitization of peripheral and central nervous system pain-processing pathways (31), neuroplasticity (32), and dysfunction of the inhibitory neural descendent system (33) may be present. Implicated risk factors are anatomic factors (e.g. skeletal and occlusal relationships), pathophysiologic factors (*e.g*. trauma to the joint and muscle, bone and connective tissue disorders, hormonal differences) and psychosocial factors (*e.g*. depression and anxiety, emotional and perceptual responses to psychologic stressors) (34, 35).

In a study from 2007, Slade *et al.* concluded that depression, perceived stress and negative mood predicted twofold to threefold increases in new-onset TMDs (36). A relationship of this kind has also been established for certain subgroups of TMDs by both psychometric (37) and experimental methods (38) in other studies. Significantly elevated daytime plasma cortisol levels in subjects with TMDs have also been found (39). Fillingim *et al.* recently concluded that perceived stress, previous life events and negative affect are good predictors of TMD incidence, but somatic symptoms are also strongly associated with TMD onset (40).

Interrelated conceivable mechanisms between TMD patients and those who report suffering from other chronic pain conditions, e.g. fibromyalgia, whiplash, irritable bowel syndrome, low back pain and chronic fatigue syndrome, also exist (27, 41, 42).

In a publication from the large OPPERA case control study, Smith *et al.* characterized the biologic pathways through which genetic variations causally influence TMD risk and suggested that neurotransmitters, genetic and epigenetic factors (*i.e*. genomic DNA modifications that alter gene expression) could interact to make their respective contribution to the development of chronic TMD pain (43).

During the last few decades, there has been an acceptance of a multifactorial etiology and the biopsychosocial model of TMD pain proposed by Dworkin and coworkers has become widespread. Slade *et al.* recently stated that it is inaccurate to regard TMD only as a local orofacial pain condition because of its complexity and multiple causes (44).

TMDs and bruxism

Self-reported SB is regarded as a risk factor for painful TMDs (45, 46), but, in another study with polysomnography measurement, there was no evidence of an SB and TMD relationship (47). In other polysomnographic and electromyographic studies, there is a more obscure association between SB and TMDs and a negative association has even been observed by Rompré *et al.* (48). In this study, subjects with pain experienced fewer bruxism episodes measured with electromyography (EMG) compared with subjects without pain. The relationship between awake bruxism, SB and TMDs is complex and there are conflicting views in the literature on whether or not there is a connection (49, 50).

1.1.4 TMD/osteoarthritis

Description of the condition

Osteoarthritis (OA) is the most common degenerative disease in the TMJ (51) and affects the bone, supporting tissues and articular cartilage of the joint. The temporal and condylar articular surfaces are covered with a fibrocartilage and differ from those of other synovial joints (52). The synovial fluid in the joint both lubricates and repairs the fibrocartilage and TMJ disc that are largely acellular.

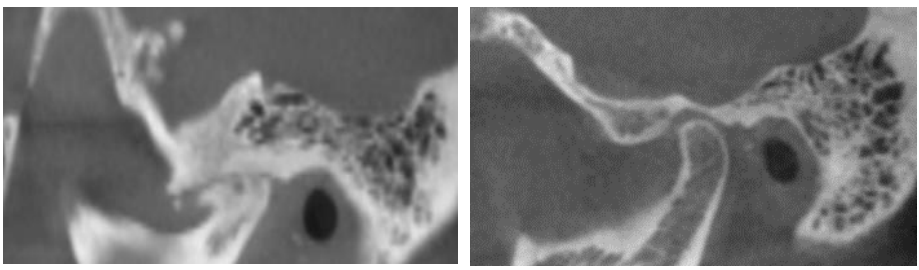

Figure 1. Radiography with (left) and without (right) OA in TMJ.

OA is radiographically characterized by the degeneration of joint cartilage and osseous erosion, sclerosis, flattening of the articular surface, osteophyte formation and the development of subchondral bone cysts (*Figure 1*).

The most common signs and symptom are joint pain that reduce function and worsen with activity. Pain on palpation of the joint is also common but not specific to OA. For RDC/TMD, in addition to pain of joint origin, TMJ noise (crepitus) with jaw movement or function or/and radiologic signs of arthrosis are also required. In addition to pharmacologic treatment, management options include the control of contributory factors, cold or warm packs, occlusal appliances and physiotherapy as a first-choice approach before surgical modalities such as arthrocentesis and arthroscopy (53). In recent years, studies have concluded that women with OA, at least Chinese women with knee OA, have greater pain severity and also run a greater risk of depression compared with men (54). Rosemann *et al*. also found an increased prevalence of depression among persons with OA in Germany, but gender was not a predictor (55).

Epidemiology

The wear-and-tear deterioration starts in the early 30s (56) and OA becomes more common with age. After the age of 50 years, more women than men are affected (57) not only in the TMJ but also in the knees and hands (58). The TMJs are affected, with a prevalence of 5%-16% in clinical cases referred for the treatment of TMDs (59, 60).

Etiology

Excessive mechanical loading (*e.g*. bruxism) or loading without adequate lubrication, as well as disc displacement together with synovial fluid alterations, can lead to the loss of joint cartilage and the breakdown of underlying bone. (56). The onset of OA is often insidious and the state tends to be chronic. OA is classified as a low degree inflammatory process that results from a degenerative condition of the joint structures (1, 56). OA has also been suggested to be a chronic non-inflammatory disease (61). The etiology is complex and multifactorial, with genetic, biologic, and biomechanical components (62). Resent research suggests that stress-induced and pro-inflammatory mechanisms underlie the pathogenesis of OA (63).

1.1.5 Pharmacotherapy for TMDs

Several different treatments are conventionally prescribed, with variable success, in the diagnosed subclasses of TMDs. The goal of the treatment is to improve jaw function and relieve pain. Pharmacological therapy is most frequently used in the acute situation and represents one of the primary interventions for TMDs. Several treatments are reserved for short-term use due to a risk of tolerance development, toxic side-effects and adverse events.

Combination of multiple pharmacologic treatments is a frequently used strategy, often in combination with behavioral and dental (stabilization splint) strategies, as well as physiotherapy. Early pain medication is recommended to prevent the development of chronic pain in modern pain control concepts.

Acetaminophen (paracetamol)

Acetaminophen represents a first-line treatment in several pain conditions including TMDs. However, the pain-relieving effect is frequently insufficient, especially in chronic pain in the hips or knees (64). Acetaminophen has an antipyretic effect but lacks anti-inflammatory properties. When correctly used, side effects are uncommon and the drug is effective in chronic pain. The recommended daily dose (500 mg x 6 or 1,000 mg x 4) is close to the maximum dose (4,000 mg/day) and care must be taken to avoid toxic levels that can cause irreversible liver damage.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are usually subcategorized into non-selective and selective cyclooxygenase enzyme 2 (COX-2) inhibitors. Non-selective COX inhibitors affect both COX-1 and COX-2 enzymes (65). On the other hand, the selective COX-2 inhibitors only block the COX-2 enzyme.

NSAIDs are used for acute inflammatory pain. The effect has been shown to be superior to that of both aspirin and acetaminophen and combinations. However, there is no support in the literature for a benefit in chronic orofacial pain (66). Singer *et al.* concluded that the analgesic effect of ibuprofen (600 mg x 4) was comparable to that of placebo in a group of chronic myogenous pain patients (67). Generally, reviewers conclude that NSAIDs are ineffective as monotherapy for chronic pain. This is supported by List *et al*. in a review from 2003, summarizing that the daily use of NSAIDs in patients with chronic TMD pain had only limited efficacy (12). However, another study confirmed significant pain relief and also a significant improvement in the range of mandibular motion with naproxen (non-selective COX inhibitor) for the treatment of painful TMJ disc displacement with reduction compared with both placebo and celecoxib (selective COX-2 inhibitor). Naproxen was well tolerated during six weeks at the given prescription (500 mg twice daily) (68). NSAIDs are often used in the treatment of pain in OA and are acceptable in terms of addiction and tolerance. In a study comparing stabilization splints and diclofenac sodium (50 mg x 3), both treatments produced a significant reduction in the symptoms of TMJ OA within three months (69). Despite this, NSAIDs are not recommended for long-term use because of an effect on renal disease and cardiovascular events and a potential toxic effect on the gastrointestinal tract (70).

COX-2 inhibitors have not been shown to relieve TMD pain more effectively than the non-selective NSAID inhibitors (68) and attention must be paid to this, since there is an increased incidence of cardiovascular events in long-term use. However, they can be considered as an alternative in some patients for the treatment of chronic TMD pain since they appear to cause fewer gastrointestinal complications (70, 71).

Opioids

The use of opioids for TMDs is controversial. Morphine and codeine have potent analgesic effects and may have a place in the acute setting of severe cases. Newer opioid agonists like oxycodone have also been applied in patients with severe pain. However, the potential risk of addiction and the occurrence of side-effects are not negligible for these drugs (70). Opioids can therefore only be advocated under appropriate supervision for long-time administration for patients with severe TMJ dysfunction when all other treatments have been failed (72).

Evidence of an analgesic effect from the intra-articular administration of morphine in the TMJ in patients with OA is inconclusive. In two studies, no significant short-term analgesic effect was seen. Pain intensity at maximum mouth opening, measured using a visual analog scale (VAS) pain score, was significantly reduced but not to a clinically relevant extent at a one-week follow-up following injection with 0.1 mg morphine (73, 74). In another study, Ziegler *et al*. showed that intra-articular morphine application in the TMJ, at a dose of 10 mg with three injections, showed an extended effect that remained one week after the third injection (75).

Antidepressants

It has been demonstrated that non-depressed chronic pain patients may benefit from antidepressant medication such as amitriptyline in low doses (25 to 75 mg daily). The analgesic effect of antidepressants is seen at doses lower than those used in the treatment of depression and the effect can be differentiated from placebo in the treatment of chronic orofacial pain (76). In a study from 2000, Plesh *et al.* reported a significant reduction in pain scores after six weeks but also after one year (77) and a recently published open study concluded that amitriptyline had a good effect on myofascial pain (78). Tricyclic antidepressants with both serotonergic and noradrenergic effects appear to be the most suitable for orofacial pain conditions, but care must be taken with regard to the dose-dependent side-effects and adverse events.

Benzodiazepines

Several benzodiazepines have sedative properties which may be used in chronic orofacial pain of myogenic origin. Singer and Dionne have shown significantly better pain relief with diazepam (10 mg/d increasing to max 20 mg/d) compared with placebo or ibuprofen in patients with chronic orofacial muscle pain (67). In a double blind randomized clinical trial Pramod *et al.* observed a significant difference between diazepam and placebo in mouth opening reduction and in masticatory muscle tenderness, in the short term (79). An older double-blind pilot-study with clonazepam in patients with chronic myofascial pain showed a superior effect compared with placebo (80), but in another study triazolam failed to reduce pain but improved sleep quality (7). The duration of the medication should not be longer than a few weeks because of the risk of adverse effects such as abuse and the development of dependence (70).

Muscle relaxants

Muscle relaxants such as carisoprodol reduce muscle tone without affecting motor function by acting centrally and are reported to be superior to placebo in the treatment of acute musculoskeletal disorders but not for chronic conditions (81). There is no evidence relating to the use of the muscle relaxants cyclobenzaprine or tizanidine for reducing TMD pain of myogenous origin in a recent randomized controlled clinical trial (82). Severe side effects such as sedation and depressive symptoms could appear and should be considered, as well as the abuse potential. In Sweden, carisoprodol has been taken off the market.

GABA-ergic drugs

Central muscle relaxants such as GABA-ergic drugs are often used in the treatment of spastic movement disorders, such as epilepsy in association with cerebral palsy (CP). Baclofen is a GABA agonist and tiagabine is a selective GABA reuptake inhibitor. Both suppress the motor activity, characteristic in spasms. Tiagabine may suppress SB in severe cases (83), but the data are still incomplete.

Botulinum toxin-A (BTX-A)

BTX-A is a peripheral muscle relaxants acting as a neuromuscular blocker. The neurotoxin, which is produced by the anaerobic bacterium, Clostridium botulinum, and reversibly blocks the release of acetylcholine at the neuromuscular junction. There are several subtypes of toxin, but the most commonly used is BTX-A. BTX-A is stored frozen in a vial and mixed with saline solution before use, according to the manufacturer's guidelines. The number of injection sites and the doses are usually determined by the size of

the muscle. The dose is also established by the diagnosis. The effect usually occurs after a couple of days to two weeks, with relatively few side-effects and adverse events. The effect of BTX-A is reversible and, when correctly injected into the muscle, function is partially blocked for two to three months. Injections should not be given more often than once every three months in order to avoid the development of antibodies against the toxin (84).

BTX-A has been used in the care of patients with CP to reduce spasticity in the upper and lower extremities and this application has been successful for a long time (85). However, in orofacial pain conditions the results appear to be more equivocal. Early case reports of secondary masticatory muscle spasm (86) as well as hemifacial spasm often describe successful treatment with BTX-A (87-89). Guidelines for the upper and lower extremities have been developed and evaluated with good results and BTX-A has been shown to be well tolerated and safe (90, 91). In a pilot study, Manzano *et al.* used BTX-A with positive results to alleviate spasticity and bruxism in the masticatory muscles in young patients with CP (92). In a study from 2000, Barwood *et al.* (93) injected BTX-A to reduce spasticity in very young children (mean age 4.7 years) with CP and noted a considerable reduction in the pain score compared with placebo. In a review of cervical dystonia and chronic facial pain associated with muscular hyperactivity, local injections with BTX-A were reported to be both safe and significantly better than placebo (94), but the effect of BTX-A was questioned in another study of treating chronic myofascial TMD pain (95). Many open-label and uncontrolled studies support BTX-A for TMDs (96-99) but the results are less positive in randomized, blinded and controlled trials (95, 100, 101). In conclusion, there is insufficient data to systematically recommend BTX-A treatment of chronic TMD pain (102).

Corticosteroids

Methylprednisolone or betamethasone are often used for intra-articular injections in small joints as well as in the TMJ, preferably in the superior joint space. Corticosteroids are usually mixed with a local anesthetic in order to obtain immediate pain relief. Both the duration and extent of the pain relief appear to be brief, at least following injections in the knees (103). Corticosteroid injections have been shown to be effective on pain and dysfunction related to inflammatory TMJ OA pain conditions (104). In a review from 2012 de Souza *et al.* concluded that there is weak evidence to support that sodium hyaluronate and betamethasone have similar effects in reducing pain and discomfort (53).

The anti-inflammatory mechanism of action of corticosteroids is not fully understood but may include prevention and inhibition of proteolytic enzymes

(105). In addition, histamine activity, mast cell activity and other cellular responses are inhibited. It has also been shown that corticosteroids block neuropeptide release (106) and reduce the synthesis of prostaglandin E in TMJ OA. Side-effects can be considerable after systemic administration but this is not the case with a limited number of intra-articular injections in the TMJ. Moreover, local side-effects as a result of intra-articular injections are rare when the recommended dose and duration are respected (107). Local skin atrophy can occur, but, in these cases, the injections were incorrectly performed.

Sodium hyaluronate

Sodium hyaluronate, commonly referred to as hyaluronic acid, has anti-inflammatory properties and is normally found in the synovial fluid where it acts as a lubricant. The mechanism of action is not fully known, but sodium hyaluronate may normalize the biochemical conditions in the joint. It is suggested that the injections should be given in series of three, one month apart. Very few side-effects have been reported. In a study by Björnland *et al.,* it was stated that both sodium hyaluronate and corticosteroid injections reduced pain and improved function in patients with OA. Sodium hyaluronate was significantly more effective in pain relief than corticosteroids (108). A review from 2003 stated that sodium hyaluronate had the same effects as corticosteroid injections in terms of symptom improvement, reduction of clinical signs and overall conditions of the disorders, in both the short term and the long term. However, the evidence was insufficient to either support and reject the use of sodium hyaluronate for treating patients with TMDs (109). Recently (2015), an RCT concluded that the effect of both high- and medium-molecular-weight sodium hyaluronate in single-session interventions on pain levels in TMJ was negligible. However lavage plus viscosupplementation was significantly superior in this study (110). In a meta-analysis from 2012 of viscosupplementation for OA in the knee, it was concluded that clinical benefits in terms of improved function or reduced pain could be detected (111).

Glucosamine sulfate

Glucosamine sulfate is an endogenous substance that occurs naturally in the articular cartilage. The side-effects are few and often mild. In-vitro work has shown that it can alter chondrocyte metabolism (112), but the mechanism of action is not known (113). Glucosamine is taken as a dietary supplement and the usual recommended dose is 500 mg three times daily. A study by Reginster *et al.* supported the effect of glucosamine in knee OA (114) and, in a review from 2012, de Souza *et al*. concluded that glucosamine appeared to be equally effective as ibuprofen for the management of OA in the TMJ (53). There is, however, equivocal evidence that glucosamine benefits pain and function in

OA in other joints (115). Wandel *et al.* concluded that glucosamine does not reduce joint pain in the hip or knee (116). To summarize, glucosamine has not been shown to have clinically relevant benefits and it is not recommended in guidelines, at least not for knees (117).

Topical medications

The most common topical medications are ointments containing capsaicin and NSAIDs. Capsaicin has been shown to be effective in the pain relief in OA (118, 119). The results for NSAIDs are more contradictory, but the adverse gastrointestinal events caused by orally administrated NSAIDs appear to be reduced and topical medications can be considered safe (120, 121).

1.2 Sleep

1.2.1 Definition and description

Sleep is defined as a physiologic and behavioral state characterized by partial isolation from the environment (122). Most of us have a natural circadian rhythm of a 24-hour cycle driven by genes and synchronized by the light. We sleep for an accumulated time that corresponds to one third of our lives, but the ideal sleep time differs between people. A good night's sleep is often associated with having slept continuously throughout the night. Adults usually sleep for between six and nine hours, but there is a wide variation. Too short (and too long) sleep time are expected to have undesirable health effects such as cardiovascular disease (122). Important functions of sleep include physical recovery, biochemical refreshment, reset or protection of immune function, learning and memory consolidation (122). Various patient-reported outcome measures (PROMs) such as sleep quality, sleepiness, insomnia severity, medical ailments and general quality of life can be evaluated by validated questionnaires (see pages 32-33).

Sleep occurs in cycles and most of us produce three to five sleep cycles each night. Rapid eye movement (REM) sleep and non-REM (NREM) sleep represent the two principal states of sleep. REM sleep is frequently associated with dream activity and is also a stage of muscular hypotonia. NREM sleep includes three stages, N1, N2 and N3. Each sleep cycle is approximately 90 minutes and the sleep stages occur in the following order: N1 – N2 – N3 – N2 – REM (123). N1 is a period between wakefulness and sleep and is classified together with N2 as light sleep. Approximately 25% of sleep time consists of REM sleep and only 5% of N1. N2 is the most common sleep stage which accounts for 45% of the total sleep cycle. Stage N3 is usually associated with deep sleep and dominates the early part of the sleep period and ends up

accounting for 25% of total sleep time. More light sleep and REM sleep are seen before awakening and tend to increase during the night (124).

1.2.2 Sleep disorders

Description of the conditions, epidemiology and etiology

Incomplete and fragmented sleep may cause excessive daytime sleepiness, fatigue, lack of attention, irritability, impaired memory and a need for restorative sleep. Several sleep disorders, including insomnia, parasomnias, respiratory disturbances during sleep, movement disorders and pain have been classified. Sleep bruxism (SB) and periodic limb movements (PLM) represent sleep-related movement disorders and it cannot be ruled out that both conditions share similar pathophysiological mechanisms (125, 126). Both conditions usually occurs during sleep stages N1 and N2 and are associated with arousals.

Restless legs syndrome/Willis-Ekbom disease (RLS/WED) is a fairly common, clinically evaluated, neurologic condition and can appear both while awake and during sleep. Patients with RLS/WED often report an urge to move the legs when they are at rest. The main characteristic of RLS/WED is a worsening of the symptoms in the evening and during the night (127). The prevalence is approximately 5% to 10% and it increases with age and. RLS/WED is twice as common among women compared with men (128). Lavigne and Montplaisir suggest a genetic component for the syndrome (125). It has been clearly established that iron-deficiency anemia can cause secondary RLS/WED and treatment with oral iron can resolve the symptoms for some patients (129). Another supported hypothesis is that dopamine agonists are involved in the pathophysiology of RLS/WED. Dopaminergic agonists show a good therapeutic effect in RLS/WED and represent the treatment of choice. Other medications prescribed to treat RLS/WED include opioids, anticonvulsants and benzodiazepines (128).

Periodic limb movements (PLMs) are described as rhythmic extensions of the big toe and dorsiflexion of the ankle, with occasional flexions of the knee and hip (128). The cut-off criterion for a pathologic condition is PLM in a sleep index higher than 15 for older and 5 for younger persons, for the whole night of sleep (128). PLMs are overrepresented in patients with RLS but the exact mechanistic association between the two conditions is unknown. PLMs are more likely to occur during the first third of the night, they rarely appear in association with REM sleep and they specifically tend to appear in association with stage shifts during the sleeping period.

Sleep-disordered breathing is divided into obstructive and central events. Obstructive sleep apnea (OSA) is defined as an obstruction in the upper airway, while central sleep apnea appears as a reduced brain signal to drive respiration. OSA is a respiratory disturbance and is characterized by daytime sleepiness, snoring and episodes of total (apnea) or partial (hypopnea) obstruction of the upper airway for 10 seconds or more during sleep. Repetitive obstruction of the upper airway often results in oxygen desaturation and arousals from sleep (130, 131). The severity of OSA is assessed using the apnea-hypopnea index (AHI) which represents the number of apneas and hypopneas per hour of sleep (n/h). The critically applied cut-off criteria for mild, moderate and severe OSA are an AHI value of 5 to < 15, 15 to < 30 and ≥ 30 events, respectively. OSA is linked to comorbid conditions including diabetes mellitus, metabolic disorder, hypertension, cardiovascular disease and stroke. The prevalence of sleep apnea in the general population is estimated at 9% in middle-aged women and 24% among middle-aged men based on an AHI cut-off of ≥ 5/h (132).

Individuals with SB may have sleep apnea (133), but the two conditions are not likely to share common mechanisms (134). The proposed relationship between SB and sleep apnea is complex (135), but most of the individuals with SB have a normal sleep organization and macrostructure (136, 137). Yatani *et al.* have described a frequent use of sleep medication in TMD patients (138). There are also reports that individuals with sleep disturbances have twice as many jaw pain symptoms as the general population (139) and, in a recent study from the OPPERA cohort, Sander *et al*. found that disrupted sleep and OSA was significant associated with an increased incidence of TMD (140, 141).

Sleep and sleep disorders are routinely assessed with a polysomnographic (PSG) recording, which includes electromyography (EMG), electroencephalography (EEG) and electrooculography (EOG) (142). PSG recordings can be performed in a sleep laboratory or in an ambulatory home setting. (*Figure 2).*

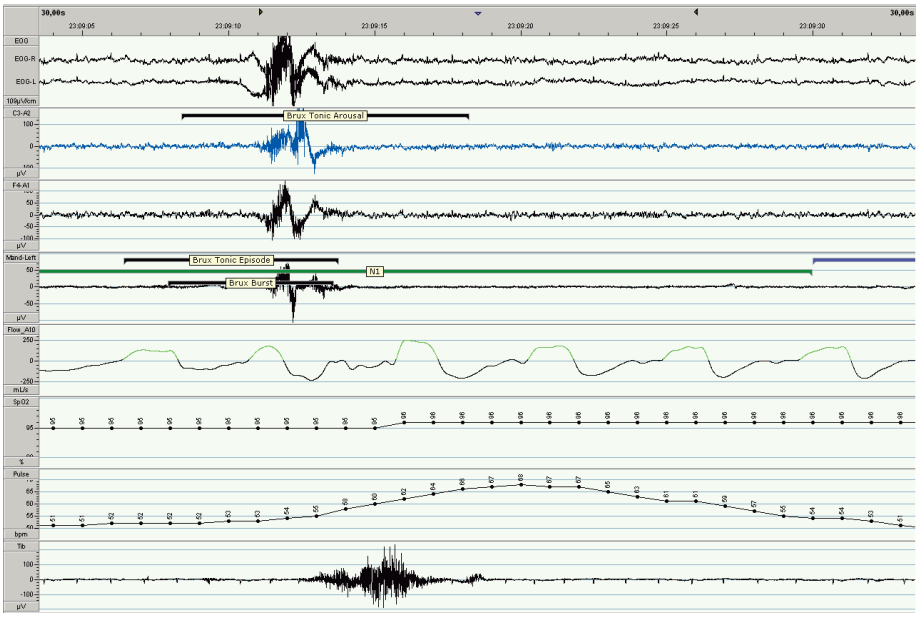

Figure 2. A 30 second recording of biological signals in a PSG. The following channels are shown from top to bottom; eye movements (EOG right and left), EEG activity (two channels C3-A2 and F4-A1), masseter muscle EMG (Mand left), nasal airflow (Flow), oxygen saturation (SpO2), pulse rate (Pulse) and tibial muscle EMG (Tib). The recorded event is a tonic bruxism episode with a burst and a brief arousal from sleep.

1.2.3 Bruxism

Description of the condition

By consensus, bruxism has been defined as a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible whilst asleep and/or during wakefulness (8, 10). There are suggestions that sleep and awake bruxism are two different disorders based on different stages of consciousness (143) and with different etiology and pathogenesis (35, 144, 145). Tooth grinding dominates during sleep, while clenching is dominant when awake (48, 146). Awake bruxism is mainly related to stress and anxiety expressed as a jaw muscle clenching habit or tic (143), but otherwise healthy adults and children with SB also appear to have higher stress scores, even if strong evidence is absent (147). Up to one third of individuals with SB may also have daytime bruxism (146, 148). SB has been associated with several deleterious clinical consequences in dental and related structures, such as abnormal tooth wear, fractured teeth, tongue indentation,

jaw muscle pain, morning headache, masseter muscle hypertrophy, reduction in salivary flow and burning tongue (149).

A history of teeth grinding is frequently reported by the patient's bed partner. Painful jaw muscles upon awakening or tooth wear are not the clinically most reliable signs of SB. In fact, it is desirable that SB is quantified by detection of rhythmic masticatory muscle activity (RMMA) in PSG recordings including EMG (143, 150). RMMA is defined as chewing-like rhythmic jaw movements with a frequency of about 1 Hz (143). Most of the rhythmic muscle activity occurs in episodes and often in clusters, in light stages of non-REM sleep. They may be associated with brief natural sleep arousals preceded by a shift in cardiac autonomic and respiratory activity (137, 145, 147, 151, 152). SB is most likely concomitant or secondary to alteration in sleep patterns and does not trigger sleep arousals (143). SB according to sleep-laboratory criteria is characterized by an EMG amplitude reaching at least twice the background activity and a period of at least three seconds of stable background EMG before a new episode of bruxism takes place (153). The episodes are characterized according to three forms (burst); sustained (tonic) jaw clenching, repetitive brief (phasic) activity or mixed (both tonic and phasic) *(Figure 3)*. Sustained episodes are defined as bursts if their duration is > 2 seconds. Repetitive brief episodes are defined if each burst duration is ≥ 0.25-2 sec and ≥ 3 elevations occur in a regular sequence (136). The SB frequency is low if there are two to four episodes/h of sleep or less than 25 bursts/h of sleep. These values are often used as polysomnographic cut-off criteria for SB with or without an audio recording of a minimum of two audible tooth-grinding episodes per night (136, 153, 154). PSG is the most reliable method for diagnosing SB, as well as other sleep disorders such as obstructive sleep apnea-hypopnea and periodic limb movements (143). Other orofacial activities during the night, such as sleep talking and coughing, are common and need to be excluded before SB can be diagnosed (155).

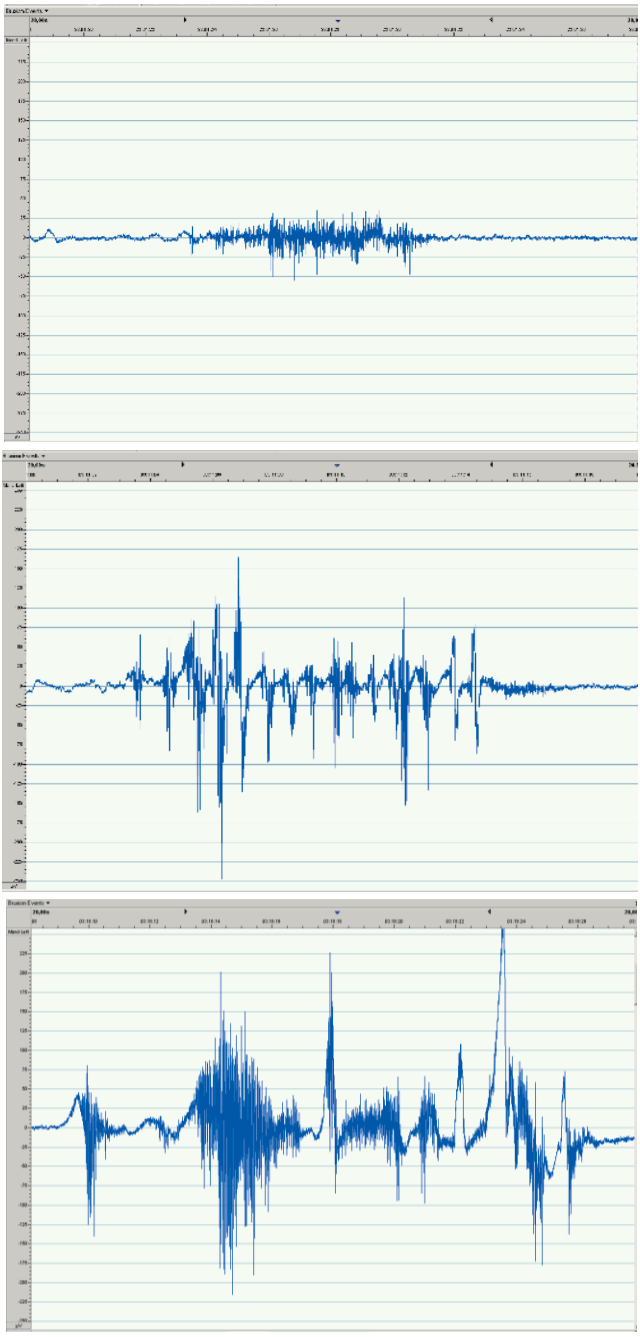

Figure 3.Three 20 second illustrations of PSG recorded (masseter muscle EMG) episodes of sleep bruxism. Depicted are, from top to bottom three types of bursts; tonic, phasic and mixed. A time scale is provided in each recording.

Epidemiology

Bruxism can be diagnosed based on self-report, by a bed partner or parents as witnesses, by clinical inspection or objectively by PSG and EMG. Lobbezoo *et al*. defined and proposed a grading system of 'possible', 'probable' and 'definite' sleep or awake bruxism (8).

- Possible; based on self-report by means of questionnaires and/or the anamnestic part of the clinical examination
- Probable; based on self-report plus the inspection report of the clinical examination
- Definite; based on self-report, a clinical examination and a polysomnographic recording preferably with audio/visual recordings

In a large population-based, cross-sectional telephone survey, self-reported, sleep-related tooth grinding was observed at least weekly in more than 8% of the interviewees (156). There is a natural variability in bruxism over time (157), but this appears to be less pronounced among heavy bruxers (158). In a general population study with objective confirmation of SB by overnight PSG and masticatory muscle EMG recordings (159), there was a 7% prevalence (160). Moreover, the prevalence of SB was comparable between men and women and was found to be 14-20% in childhood, 12% in teenagers and adults and decreases with age to reach 3% in the elderly (125, 161-163).

Etiology

The International Classification of Sleep Disorders (ICSD) from the American Academy of Sleep Medicine (AASM) categorizes SB as a sleep-related movement disorder associated with excessive sleep arousal activity (10). Klasser *et al.* suggested that SB has a multifactorial etiology, involving complex multisystems and physiologic processes (164). The exact causes and pathophysiology of SB are still unclear (145). SB can be classified into primary and secondary forms (147). Primary SB is idiopathic, broad and non-specific, while secondary SB is related to a medical condition or the use of medication (134, 143). Common comorbidities of SB are orofacial pain, as well cerebral palsy (CP). Risk indicators linked to SB can be divided into morphologic, psychosocial, physiologic and exogenous factors (165). Anatomic and morphologic causes play a minor role in the etiology and current reports state that bruxism appears to be regulated mainly centrally and not peripherally (144). Physiologic and biologic factors appear to be important in the etiology of SB. This includes traumatic injury, sleep related disorders (arousals and sleep-disordered breathing) and neurochemicals (catecholamines). Exogenous factors of significance are drug intake or withdrawal, *e.g.* neuroleptics that can

induce oral tardive dyskinesia and grinding, but also alcohol, nicotine and illicit drugs like ecstasy. Psychosocial problems such as anxiety, life stress and personality could be associated with SB in some patients. Genetic factors (hereditary component) have also been increasingly linked to the genesis of SB (165, 166). Indeed, bruxism tends to "run in families" (167). Certain neurotransmitters (serotonin, dopamine, noradrenalin, histamine) may play an indirect role in SB and studies on this topic have implied an alteration in central dopaminergic function in the development of sleep bruxism (144, 168). The sleep-related incidence and repetitive occurrence of SB bear similarities to PLM (125, 126) and responsiveness to dopaminergic agents in both conditions has been suggested. (49, 169). Hence, and in conclusion, it is evident that the etiology of SB is multifactorial and it cannot be explained by a single or simple mechanism.

1.2.4 Pharmacotherapy for SB

There is no accepted single treatment for SB apart from strictly dental protective measures (149, 170, 171) and perhaps behavioral strategies. Stabilization splints reduce tooth damage but are not recommended for patients with sleep apnea, because they can aggravate the respiratory disorder (172). Various pharmacologic therapies have been explored in bruxism and various drug classes have been associated with either a reduction or an exacerbation of bruxism (173). There is currently insufficient evidence of the effectiveness of pharmacotherapy for the treatment of SB (174).

Since stress and anxiety have been implicated in the exacerbation of bruxism, sedative and anxiolytic drugs have been suggested as therapeutic options. Single case reports on buspirone (anxiolytic psychotropic drug) showed conflicting results (173), while clonazepam (benzodiazepine) reduced bruxism in controlled trials (175, 176). However, the level of evidence remains proportionally weak and at least benzodiazepines have been associated with a risk of addiction. Tricyclic medication, *i.e.* amitriptyline, was reported to be ineffective in a cross-over, double-blind clinical study (177) and cardioactive sympatholytic medication such as propanolol (beta-blocker type) did not significantly influence SB. Clonidine, a well-known antihypertensive medication, reduced bruxism but with a severe risk of hypotension in the morning (178, 179). Another compound with a reported modest influence on SB in a controlled trial is levodopa (L-dopa) (180). Bromocriptine, a direct dopamine agonist, had no obvious effect (181) while pergolide, another dopaminergic agent, showed positive effects in a case report (169). A recent study by Mayer *et al.* proposed a possible dysfunction of central dopamine mechanisms in SB (182). Pramipexole (PPX) is a dopaminagonist with affinity

to some serotonin and adrenergic receptors and with a documented good therapeutic effect in RLS/WED (183). There are no studies on the potential influence of PPX on SB. Serotonin-related medication such as tryptophan did not show any effect on SB (184). In a systematic review from 2014, Macedo *et al.* concluded that there are no statistically significant differences in jaw muscle activity or bruxism episodes per hour between levodopa, amitriptyline, bromocriptine, clonidine, propranolol or tryptophan, compared with placebo (174). When it comes to BTX-A, contradictory results were presented by Manfredini *et al.* in a systematic review from 2015 (185). Another recent study with PSG evaluation concluded that BTX-A reduces the strength but not the frequency in the jaw-closing muscles (186). There are also some case reports on severe bruxism due to brain injury with successful BTX-A treatments (187, 188). In summary, no pharmacologic treatment can be recommended for SB today.

1.3 Cerebral palsy

1.3.1 Description of the condition

Cerebral palsy (CP) is non-progressive and one of the most common physical disabilities in childhood. CP is a heterogeneous group of permanent movement disorders characterized by a motor impairment due to a malformation or lesion in the developing brain during pregnancy, childbirth, or shortly after birth (189, 190). CP is divided into three subtypes; spastic, akinetic or dyskinetic. Depending on the affected part of the body, spastic CP is divided into hemiplegic, diplegic or tetraplegc (191). Most patients with CP have spasticity with high muscle activity (approximately 80%) as the predominant symptom, but there may also be cases with muscle weakness (85). The severity of impairment can be divided into mild (walk), moderate (walking with aids) and severe (unable to walk). Motor dysfunction in the bulbar region, *e.g.* focal spasticity of the orofacial region, orofacial dyskinesia and dystonia is common and can complicate speech, chewing and swallowing. Concomitant disturbances of sensation, perception and cognition, as well as behavioral, are also common (192). These patients may also have dental problems. In addition to excessive tooth wear due to bruxism (193), there is an increased risk of TMD (194) in this group of patients compared with the general population. Neuroleptic medication may induce an even higher risk of parafunctions (195). Moreover, a reduction and change in salivation, as well as gastroesophageal reflux, can aggravate the dental attrition/erosion (196). Non-functional oral motor activity during both the day and night is common among patients with CP but also in other groups of dental patients with “special needs”. Dental

protection with conventional stabilization splints is seldom successful and daytime use might worsen already impaired speech.

Epidemiology

The prevalence of CP is two children per 1000 births (197, 198). Both bruxism and TMDs are observed more frequently in the young CP population than in an age-matched healthy group. Among children with CP, sleep-related bruxism affects up to 37% compared with 8% of the general population and TMDs are reported in up to 68% compared with 25% in the control group (199, 200). In another study of four to nine years old children with CP, bruxism was detected clinically in almost 70% and reported in 57% of interviews with guardians (201).

Etiology

Perinatal adverse events including hypoxia and infections and as well as prenatal causes such as brain malformations are risk factors associated with CP. The brain disturbances of the fetal or infant brain cause different activity limitations in muscular control. Possible mechanisms include the loss of physiologic inhibitory control of the basal ganglia. A possible genetic factor can only be seen in 2% and in most of the cases the etiology is multifactorial and complex.

2 AIMS

The overall aim of this thesis was to explore aspects of pharmaceutical intervention in temporomandibular disorders and bruxism.

Study I

- To investigate type and frequency of medication in patients referred for specialist treatment for temporomandibular disorders and compare with controls

Study II

- To evaluate the clinical effects of oral glucosamine sulfate compared with placebo on osteoarthritis in the temporomandibular joints

Study III

- To explore the effect of the dopamine agonist, pramipexole, in sleep bruxism, confirmed by monitoring of polysomnography/electromyography and compare with control conditions

Study IV

- To evaluate the effect of botulinum toxin-A injections in the masticatory muscles on objective and subjective oral functions in patients with cerebral palsy and bruxism in a placebo controlled study

3 PATIENTS AND METHODS

All four studies were prospective clinical trials. The first was an observational study. Studies II-IV were randomized and controlled to assess the effectiveness of interventions. Since osteoarthritis is often alleviated over time, a double-blind design with parallel groups was chosen in Study II. Bruxism might also vary over time, but it is in principle a chronic condition and cross-over therefore appeared to be the best design in Study III. In Study IV, a double-blind design with parallel groups was chosen again to limit the number of registrations and unnecessary extension over time for individual patients. Studies I, II and IV were based on power calculations made before the start while Study III was exploratory and no actual power calculation was performed. Since bruxism is a complex condition, Studies III and IV were an interdisciplinary collaboration between dentistry and medicine. None of the studies has received any sponsorship from the industry.

A total of 700 patients/controls and references were involved. None of the subjects has been compensated, despite several hours of dedicated participation, apart from the reference group in Study IV.

Research diagnostic criteria for temporomandibular disorders, axis I

The diagnoses according to RDC/TMD axis I were used in all the studies. RDC/TMD is a classification system with good reliability for research applications based on observable findings and standardized criteria for one or more of the diagnoses for TMDs (1). RDC/TMD, axis I is divided into three different groups corresponding to whether the patients' signs and symptoms are mainly of muscular (I), disc (II) or joint (hard tissue) (III) origin. All the main groups have subgroups which were also recorded.

- Ia: myofascial pain
- Ib: myofascial pain with limited opening

- IIa: disc displacement with reduction
- IIb:disc displacement without reduction and with limited opening
- IIc: disc displacement without reduction and without limited opening

- IIIa: arthralgia
- IIIb: osteoarthritis
- IIIc: osteoarthrosis

Temporomandibular index

The temporomandibular index (TMI) examination protocol was used in Studies III and IV to quantify the signs and symptoms of TMDs and a classification of the severity of problems with muscle and joint tenderness, mandibular movement and TMJ noise was made. The instrument is divided into the function index, with mandibular range of motion parameters, the muscle index, with masticatory muscle palpation sites and the joint index, with TMJ palpation and TMJ noise registrations. They all have acceptable reliability and clinical validity (202).

Consensus and calibration

One of two calibrated dentists conducted the clinical examinations in Studies I and II. After examination, they discussed the findings before they reached a consensus for a final clinical classification in each case.

Before the start of Study II, the reliability of the two investigators was calculated. Unassisted maximum interincisal opening measurements for 20 asymptomatic subjects, selected from the staff, were registered twice, six weeks apart, by each examiner independently. Calculated with Pearson correlation coefficients inter-rater reliability was $r = 0.98$ and $r = 0.94$, while intra-rater reliability over time was $r = 0.92$ and $r = 0.94$ respectively (all $P \leq 0.0001$).

In Studies III and IV, data was registered and evaluated by a single (BJC) investigator. There is reason to believe that the observations were made with sufficient accuracy (203, 204).

3.1 Study I: Utilization of pharmaceuticals

3.1.1 Study population and controls

A total of three hundred patients, 15 years or older, referred to the Orofacial Pain Clinic, Sahlgrenska University Hospital, Mölndal by dentists and medical practitioners, were consecutively included. They all fulfilled the criteria for RDC/TMD axis I diagnoses. Matched controls, regular dental patients, (gender and age ± 5 years) came from the same geographic area and were recruited in association with a routine examination by their ordinary dentist. No subjective

symptoms of TMD were reported in the control group, based on anamnestic questions.

Power calculation

With reference to an earlier study of diagnoses among referrals to the clinic, some 60 patients could be expected to be in the smallest of the three groups (Group III, joint), according to RDC/TMD axis I, in about 18 months. The muscle group (I) and the disc group (II) could be twice as large during the same period (59). A power calculation indicated that, if a specific medication was used by 30% of the patients and 10% of the controls in the smallest group with a sample size of 60, this would indicate a power of 0.79 at an alpha value of 0.05. A frequency of 15% and 1% respectively would result in a power of 0.85 at the same alpha value and sample size. For this reason, 300 patients were included in the study.

3.1.2 Method

Prospectively and consecutively, during a period of 19 months, patients were examined and medication data were registered by one of two specialist dentists. Patients' signs and symptoms were classified into one or more of the three diagnostic groups; muscular (I), disc (II), or joint (III), corresponding to RDC/TMD axis I. Moreover, a main diagnosis for the three groups was classified for each patient. Controls were selected and registered in parallel by a third dentist at a visit for their normal routine examination. No TMD examination was performed in the control group, but none reported symptoms when questioned. Both patients and controls were asked the same question systematically and in a standardized manner: "Do you use any medication on a regular basis including (women) oral contraceptives or other exogenous hormonal replacement?" The temporary use of pharmaceuticals was not registered.

Anatomical therapeutic chemical classification system

The anatomical therapeutic chemical (ATC) classification system is the most widely used classification system for drug utilization and it is coordinated by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology in Oslo (205). The pharmacological substances are classified into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. A three-digit code, based on FASS 2004 (Swedish drug compendium), was used.

3.2 Study II: Glucosamine sulfate

Pilot study

A preliminary study was performed to evaluate the most troublesome and important symptom of OA according to the patient. Twelve patients with diagnosed OA answered a written questionnaire on which of four alternatives was the main problem. The alternatives were: a) pain on opening, chewing, yawning and talking, b) constant pain in the jaw also during rest, c) difficulty opening wide properly and d) disturbing sounds from the joints. Since pain was rated as the worst feature by most of the patients (11/12), it was selected as the main variable.

3.2.1 Study population

Patients referred to the Orofacial Pain Clinics, Sahlgrenska University Hospital, Mölndal/Uddevalla, were selected from 1,192 referrals. Participants had to be 18 years or older and fulfilled the criteria for OA in one or both of the TMJs. The diagnosis of OA included pain and tenderness in the joint capsule and/or synovial lining of the TMJ and coarse crepitus or a degenerative condition on tomograms according to the RDC/TMD axis I, IIIb. Exclusion criteria were unwillingness to end ongoing treatment of the condition, pharmacologic treatment for any other painful condition, allergy or hypersensitivity to glucosamine or shellfish, or pregnancy/nursing.

Power calculation

The power calculation was based on the pilot study and on previously published data on TMJ/OA (206). If the primary outcome for a positive treatment effect was chosen as 25% pain relief on the VAS, fifty-two patients had to be included to attain a power of 0.80 with an alpha value of 0.05. To compensate for dropouts, sixty patients were included.

3.2.2 Method

The study patients were prospectively and consecutively included during a period of 46 months. After a clinical examination by one of two calibrated specialist dentists and a radiographic examination of the TMJ, they were diagnosed with OA in one or both TMJs (*Figure 4)*. Any ongoing treatment of the condition was stopped before inclusion in the study.

Randomization

Randomization, to receive the active drug glucosamine sulfate, or placebo, was performed in blocks of six by the hospital pharmacy and double blinded. A sequential randomization list corresponded to numbered medicine containers.

Opaque code envelopes were available for emergency situations but the need to open any of them never occurred and the code was first opened when the study was completed.

Quality control assay

The original expiration date for the active substance/placebo was exceeded during the inclusion period. The last of the 60 sets of capsules were therefore used by the pharmacist for a quality control assay and were found to be acceptable. As a result, only 59 patients were included.

Intervention

At baseline (T0), each patient was provided with a container with 126 capsules with glucosamine sulfate (400 mg) from one batch or placebo. The instruction was to use three capsules on a daily basis for a period of six weeks. All the containers and capsules were identical and manufactured by the hospital pharmacy without any industrial involvement. Rescue medicine, fifteen tablets of paracetamol (1,000 mg), were also handed out and patients were informed that they could order more tablets if needed. Remaining capsules of glucosamine/placebo, if any, as well as the consumed tablets of rescue medication were taken into account at the end of the study, after six weeks (T1).

Visual analog scale (VAS)

The patients rated the pain by drawing a cross on a 100 mm horizontal line with endpoints of “no pain” on the left and “worst possible pain” on the right respectively as an answer to the question “How would you estimate your TMJ pain during the last week?” at baseline (T0) and again a second time after six weeks at the end of the study (T1) (207). The distance from the left anchor point was measured in mm.

Verbal rating scale (VRS)

The pain was also rated in response to the above question on a VRS with seven categories (0-6): none, mild, fairly mild, moderate, fairly severe, severe and worst possible, at baseline (T0) and after six weeks (T1).

Objective assessment

Maximum, unassisted opening capacity, without and with pain, if any, was measured with a 100 mm ruler between the edges of the left maxillary incisor and opposing mandibular incisor at baseline (T0) and after six weeks (T1).

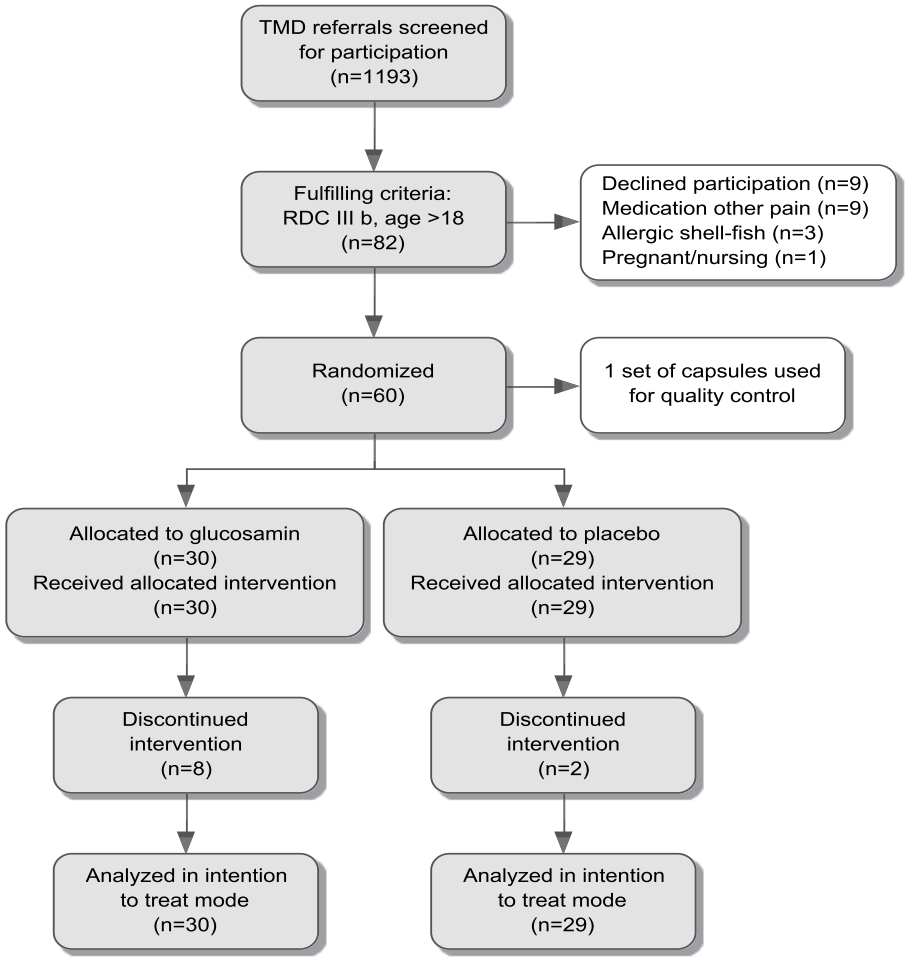

Figure 4. Flow protocol for the assignment of recruited participants to study groups and procedures in Study II.

3.3 Study III: Pramipexole

3.3.1 Study population

Twenty patients, 18 years or older, with primary SB based on self-reported symptoms, documented clinical signs and long-lasting teeth grinding certified by a bed partner or others were included from 50 invited. They were all referrals to the Orofacial Pain Clinic, Sahlgrenska University Hospital, Mölndal. Some, but not all of the 20 patients had signs and symptoms of TMD. Other common symptoms were tooth wear, multiple fractures of teeth or

restorations, signs of heavy grinding on oral appliances, teeth impression in lips or tongue, line alba in the cheeks and jaw muscle hypertrophy. Women with childbearing potential without an adequate method of contraception, breastfeeding women and patients with pharmacologic or dietary supplements which might significantly influence RLS/WED symptoms were excluded.

3.3.2 Method

Patients were prospectively included in this seven-week study, during a period of 19 months. All patients took part in a habitual night with PSG recordings, one week prior to baseline and randomization. At baseline, demographic and anthropometric data were collected, as well as a medical and dental history. Dental and orofacial examinations, including estimation of dental attrition (208), were performed by one specialist dentist. Clinical signs and symptoms were summarized in TMI. Vital signs, *i.e.* pulse and blood pressure, were recorded and blood samples were collected. Subjective assessments with PRO were evaluated using the Swedish versions of eight self-administered questionnaires under standardized conditions. In a crossover design, half the patients were randomized to medication with PPX and half to control conditions (no treatment), immediately after the baseline registration. After three weeks, the two groups changed treatment/no treatment for another three weeks. In addition to the baseline PSG, two additional full-night recordings were repeated after three and six weeks. PROM questionnaires (see pages 32-33) were completed and TMI and vital signs established after each period. The collection of blood samples was repeated after the PPX sequence *(Figure 12)*.

Randomization

Randomization was performed in a computer-generated sequence. Sealed, opaque envelopes were used by the study nurse in the allocation concealment.

Intervention

The forced titration procedure for PPX was performed according to the manufacturers' (Bluefish Pharma®) recommendations and monitored by weekly telephone calls. A medical doctor used the clinical information for dose adjustment during the three weeks if needed (*Table 1)*.

Table 1. The regimen for the study drug, PPX, to be taken daily, two to three hours before bedtime.

Product	**Titration**	
Pramipexole	Day 1 - 4	0.09 mg
	Day 5 - 7	0.18 mg
	Day 8 - 14	0.36 mg
	Day 15 - 21	0.54 mg

Objective assessments

Polysomnography

PSG including masticatory muscle EMG is an objective assessment of sleep, breathing and bruxism variables. The ambulatory PSG was recorded with an Embla® A10 system (Colorado, USA). The recordings included EEG (electrode positions C3/A2, C4/A1, O1/A2, F4/A1), EOG (right/left), EMG (submental, right and left masseter and tibial muscles) and ECG. The masseter EMG electrodes were placed on the main bulk of the muscle, according to an individual template. The recording also included a nasal pressure cannula and a thermistor for measurements of hypopneas. We also used a thoracic-abdominal respiratory effort belt for apnea and hypopnea registration and a finger pulse oximeter for oxygen saturation registration. *(Figure 5)*. All the equipment was connected to the patients at the study center in the late afternoon or evening. The patient then returned to his/her home and all PSG/EMG recordings started at approximately 10 PM. In the morning after a night's sleep, patients returned to the study center to disconnect the equipment (142, 209).

Figure 5. Portable PSG equipment connected to a study patient.

Assessments of bruxism

SB was measured and quantified by scoring RMMA on PSG recordings of EMG episodes according to AASM and Lavigne *et al.* (136, 153) but modified from the audio-video recommendation. Bruxism bursts occurred in three versions; phasic, tonic and mixed episodes (*Table 2*). Bursts of bruxism with a frequency of about 1 Hz were registered graphically using electrodes placed over the patient's masseter muscle sensing jaw muscle activity during sleep. Rhythmic masseter muscle EMG activity during sleep that reached at least twice the background activity for 0.25 sec or more was scored as a bruxism burst but there had to be a period of stable background activity for at least three seconds before a new episode could be scored. For cut-off criteria for SB see *(Table 3)*.

The number of bruxism bursts per hour was calculated, as well as the number of phasic, tonic and mixed episodes per hour. The total number of episodes per hour were calculated and used as the main outcome variables. Episodes could occur spontaneously but were more common in combination with arousals including respiratory events.

Table 2. Bruxism burst with three different versions, episodes, according to Lavigne et al., 1996 (136) and AASM, 2012 (153).

Phasic (brief)	Each burst duration is ≥ 0.25-2 sec and ≥ 3 elevations occur in a regular sequence
Tonic (sustained)	Burst duration > 2 seconds
Mixed	Both phasic and tonic types

Table 3. PSG diagnostic cut-off criteria for low and moderate to severe SB (except audio-video recordings) according to Lavigne et al., 1996 (136) and AASM, 2012 (153).

Low SB frequency	**Moderate to severe SB frequency**
< 4 episodes/h of sleep	≥ 4 episodes/h of sleep
< 25 bursts/h of sleep	≥ 25 bursts/h of sleep

Assessments of sleep and respiration

The sleep related variables assessed from the PSGs were total sleep time (TST), number of awakenings (NAW), total arousal index (TAI), awake after sleep onset, and sleep stages (N1, N2, N3, REM) as a percentage and in absolute time.

The variables for respiration assessments were AHI, the Central Apnea/Hypopnea Index (CAHI), the Respiratory Disturbance Index (RDI) and the Oxygen Desaturation Index (ODI) expressed as numbers/hour and mean saturation (mean sat) in percent. The cut-off criteria for mild, moderate and severe OSA was an AHI value of 5 to < 15, 15 to < 30 and ≥ 30 events respectively.

One single certified PSG technician scored all sleep, respiratory and bruxism variables according to the criteria given in the AASM manual for the scoring of sleep and associated events, version 2, 2012 (153). The scorer was blinded to study allocation.

Blood sampling

Serum iron, serum total iron-binding capacity and serum transferrin were analyzed and correlation analyses with reference to bruxism variables at baseline were assessed.

Patient-reported outcome measures, Questionnaires

The International Restless Legs Syndrome Scale (IRLSS) is a validated 10-item self-rating scale to assess the severity of RLS/WED. The IRLSS includes five items pertaining to symptom frequency and intensity and five items addressing the impact of symptoms on aspects of daily living and sleep. Responses are rated on a five-point scale from 0 to 4. Item scores for each feature are summarized. The following limits (0-40) are used for diagnosis: ≤ 10 mild RLS, 11-20 moderate RLS, 21-30 severe RLS, ≥ 31 very severe RLS (210).

The Epworth Sleepiness Scale (ESS) is a validated questionnaire used to determine the level of overall daytime sleepiness. The question: "How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?" is answered for eight different every-day situations (*e.g.* watching TV, reading, driving a car and so on) on a four-point scale. The item scores are summarized. A score of 10 or more is regarded as sleepy and a score of 18 or more is very sleepy (211).

The Functional Outcomes of Sleep Questionnaire (FOSQ) is designed to assess the impact of disorders of excessive sleepiness on activities of daily living. The self-administered questionnaire contains 30 items which measure five dimensions in subscales: activity level, vigilance, intimacy and sexual relationships, general productivity, social outcome. The respondents are asked to rate the difficulty performing a given activity on a four-point scale (no difficulty to extreme difficulty). For each sub-scale, an average score is calculated and the five sub-scales are summarized to produce a total score. Higher scores are associated with better functional status. Total scores range from 5-20 (212).

The Insomnia Severity Index (ISI) consists of seven self-reported items that are rated on a five-point scale of severity (score rating from 0 to 4). The items cover falling asleep, staying asleep and waking up too early. Additional items cover satisfaction with sleep, interference with daytime functioning as perceived by the patient and by others and worry/distress related to the sleep problem. The scores are summarized to yield a total score between 0 and 28. Scores below 7 indicate no clinically significant insomnia, scores of 8-14

suggest subclinical insomnia, scores of 15-21 are regarded as clinically significant insomnia of moderate severity and scores of 22-28 indicate severe insomnia (213).

The Karolinska Sleepiness Scale (KSS) is used to evaluate subjective sleepiness and assesses the momentary degree of alertness/sleepiness. The KKK consists of a nine-step scale 1=very alert to 9=very sleepy, fighting sleep (214).

The Pittsburgh Sleep Quality Index (PSQI) is an instrument used to measure the quality and patterns of sleep. It differentiates "poor" from "good" sleep by measuring seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The subject self-rates each of these seven areas of sleep by answering nine questions. The scoring of answers is based on a 0-3 point scale and a score of three reflects the negative extreme on the scale. A total score is summarized and a sum of 5 or more indicates a "poor" sleeper (215).

The Medical Outcome Study (MOS) is used to evaluate sleep quality. The MOS Sleep Scale is a 12-item self-administered scale measuring specific dimensions of sleep (problems with sleep disturbance, adequacy, somnolence, quantity, respiratory impairments and snoring). It was designed for use in patients who may have varying co-morbidities. The frequency with which each problem has been experienced during the previous four weeks is rated on a six-point scale ranging from "none of the time" to "all of the time", except sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100 with the exception of the sleep quantity subscale. All scales are scored from better (0) to worse (100), except for sleep adequacy, which is scored from worse (0) to better (100) (216).

The Short Form Health Survey 36 (SF-36) was used to evaluate general quality of health. It is a self-administered questionnaire and contains 36 items which measure eight dimensions: physical functioning (10 items), role limitation due to physical health problems (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and general mental health (5 items). There is an additional single item giving information on health change over the past year. Item scores for each dimension are coded, summarized and transformed to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). The higher value indicates a better evaluation of health (217).

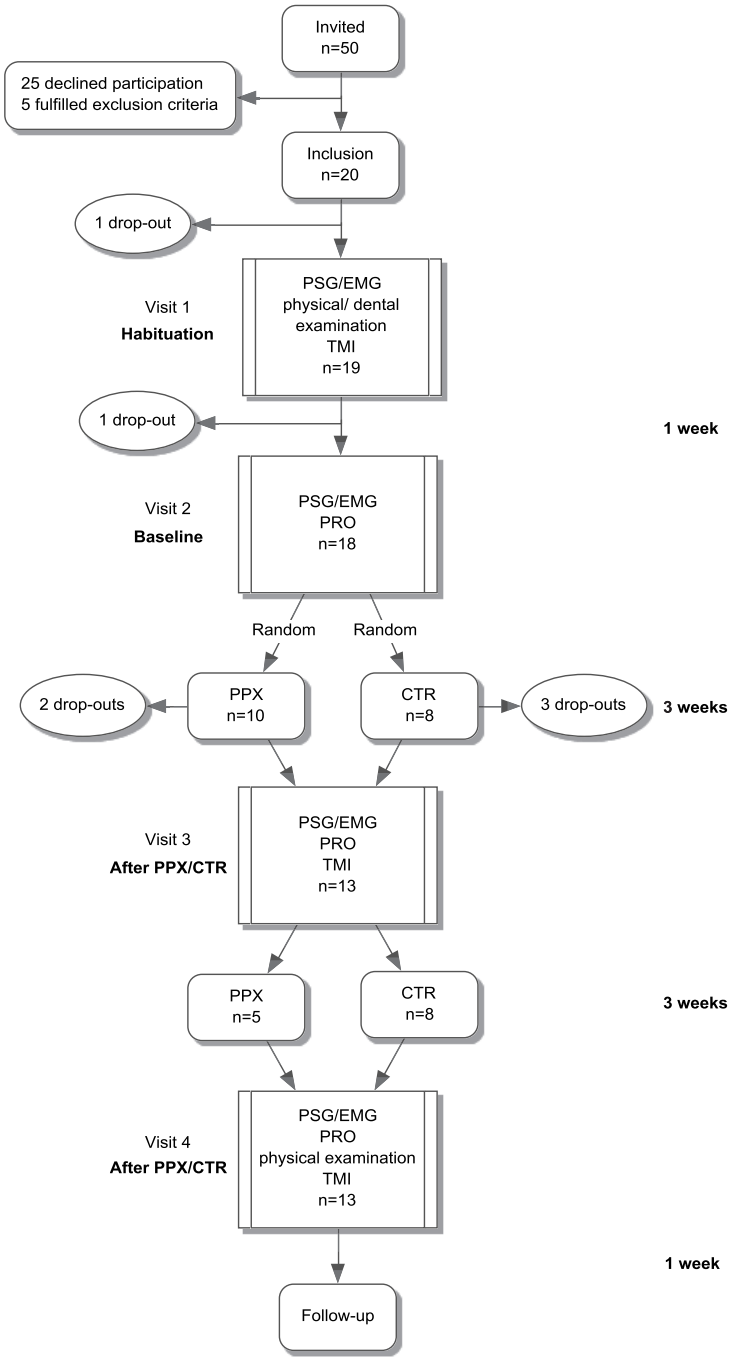

Figure 6. Flow protocol for the assignment of recruited participants to study groups and procedures in Study III.

3. 4 Study IV: Botulinum toxin-A

3.4.1 Study population and reference subjects

Patients were recruited in hospital dental clinics in the Västra Götaland Region. All patients were 18 years or older and diagnosed with CP and reported bruxism, diurnal and/or nocturnal. Other inclusion criteria were capability to read and understand information, to communicate and to make independent decisions. Pregnant or breastfeeding women were excluded. Patients with hypersensitivity to or ongoing treatment with botulinum toxin in other body parts, infections at the injection site and certain medications were also excluded.

Healthy volunteers recruited from the staff and matched for age (± 5 years) and gender with the first eight registered patients, participated as a reference group. Two registrations identical to those completed by the patients, of all variables, were performed with a four week interval.

Power calculation

A power calculation was made prior to the study to assess the adequate number of patients needed to detect a significant reduction in masticatory muscle function after injection with BTX-A. In a previous study (92), after injection with BTX-A in hypertrophic masseter muscles, the bite force decreased from a mean of 51 kg/cm² to 31 kg/cm². Based on this study, a total of 16 patients had to be included, divided into two equal groups, in order to obtain a power of 0.84 and an alpha value of 0.05.

3.4.2 Method

Patients were prospectively included during a period of 27 months. At the first visit, an informed consent form was signed after oral and written information. A medical history including medication was collected and an orofacial examination was performed. Diagnoses for RDC/TMD axis I and dental attrition/erosion were also registered and patients were randomized to receive BTX-A or control. On the following four visits at 0, 4, 12 and 16 weeks, all registrations for bite force measurements ("as hard as you can" and "as when chewing"), finger-thumb force, chewing-gum recordings (chewing efficiency) and determination of the TMI were performed. Subjective measurements were also made using the GOHAI questionnaire and by answering four questions on a VAS (*Figure 12).* All registrations were made by one blinded observer (BJC).

Randomization

Randomization was performed via a table of random numbers and numbered opaque sealed envelopes were used in the allocation. Half the patient group was randomized to receive injections with BTX-A while the other half received isotonic saline.

Intervention

After the assessment procedure, each patient was allocated to BTX-A (Botox®, Allergan) or placebo injections with isotonic saline at the first visit. The dose of BTX-A, 100 units in 1.0 ml of isotonic saline solution, was distributed with 30 units in the masseter and 20 units in the temporal muscles on each side. Placebo injections with 1.0 ml of isotonic saline solution were given in the same manner at corresponding locations. All injections were performed with EMG guidance *(Figure 7)*. Injections were performed by one neurologist on the first visit at 0 weeks and the third visit after 12 weeks. Still blinded, on visit 4, all patients were offered a BTX-A injection, on a fifth visit, eight weeks later.

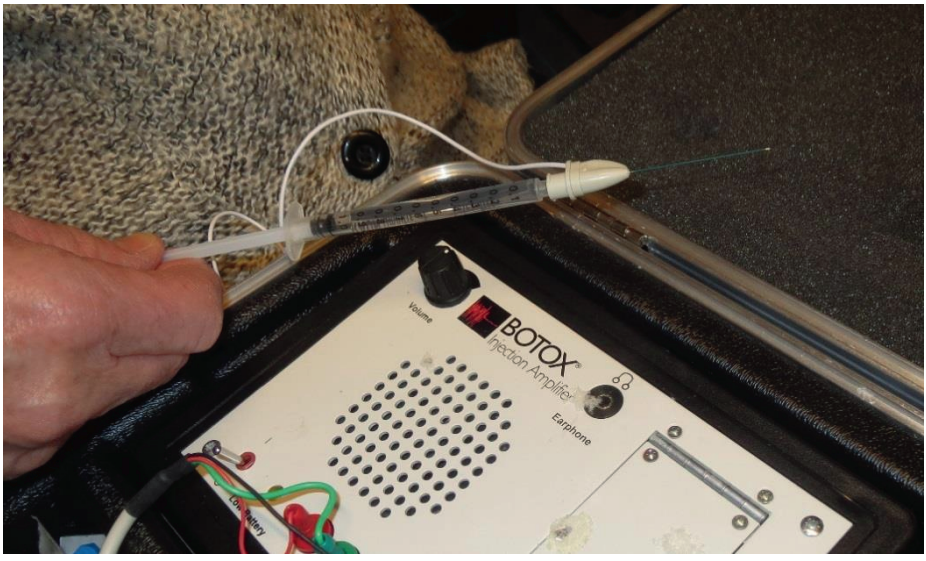

Figure 7. EMG guidance in the injection needle.

Objective assessments

Bite force

A bite fork was manufactured for the purpose to measure the bite force. The measured signals were transmitted via a cable to an electronic module where analog signals were digitalized and transmitted to a computer screen *(Figure 8)*. A standardized rubber tube covered the bite fork to protect the teeth *(Figure 9)*. To enable the duplicate placement of the bite fork, distal to the right canine, the rubber tube was marked with a cross. Each patient was first asked to "bite as hard as you can" for three seconds and the mean of the first three consecutive bites was recorded. Thereafter, each patient was asked to "bite as you would when chewing an almond" and the mean of the first five consecutive cycles was recorded. Finally, the maximum force between the index finger and thumb on the dominant hand was measured once and noted on visits 1 to 4 *(Figure 10)*.

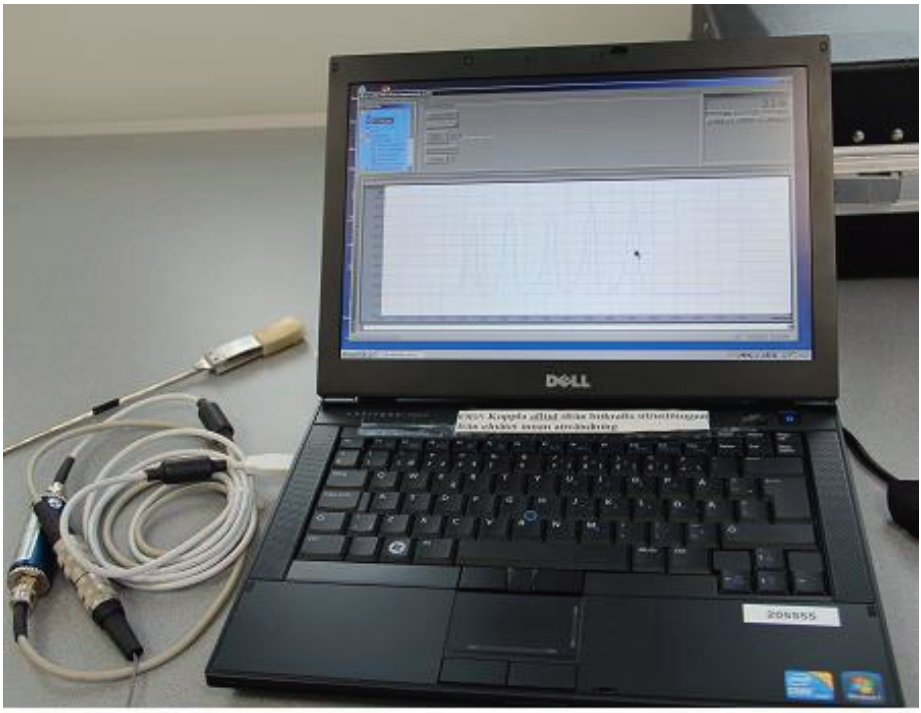

Figure 8. Bite force equipment.

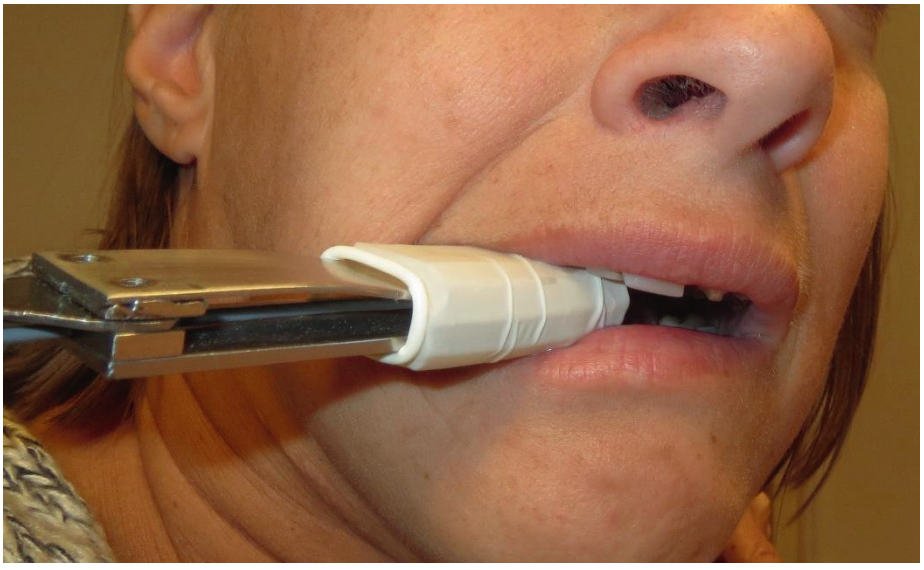

Figure 9. Bite fork placed distal to the right canine.

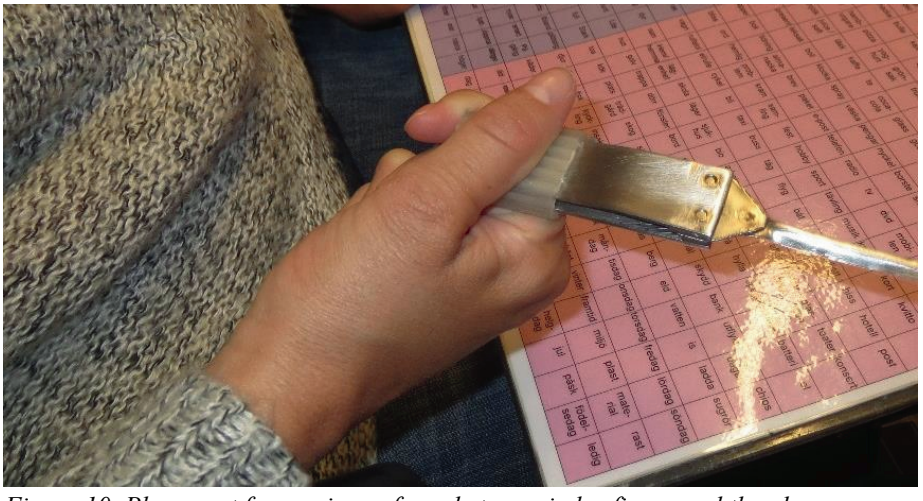

Figure 10. Placement for maximum force between index finger and thumb.

Chewing-gum

Chewing efficiency was evaluated using a color-changeable chewing gum with acceptable validity and reliability (Masticatory Performance Evaluating Gum XYLITOL®; Lotte Co. Ltd. Saitama, Japan). Patients were asked to chew 60 strokes on a standardized piece. A color scale from green to red was used to assess the color change and linked to a 0-100 mm VAS. Higher values (red) indicate more efficient chewing *(Figure 11)* (218).

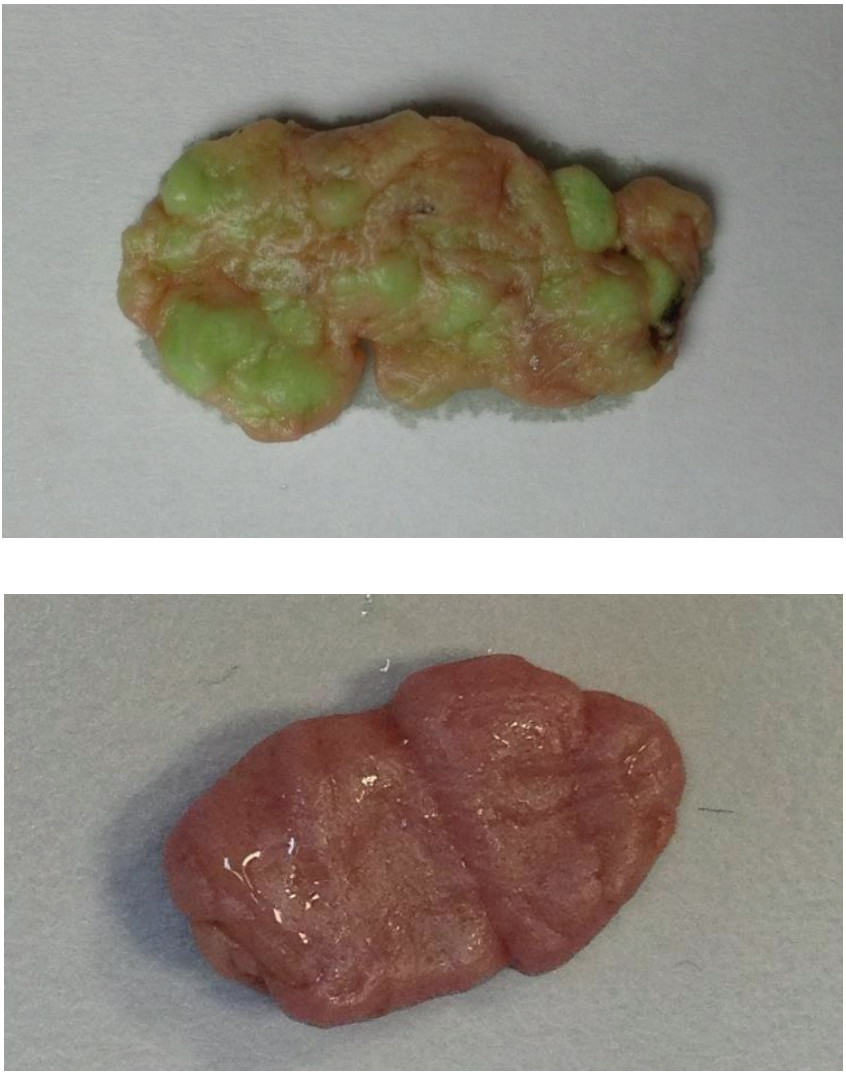

Figure 11. Different chewing efficiency evaluated with a color-changeable chewing gum after 60 strokes from one patient and one reference subject.

Patient-reported outcome measures, Questionnaires

VAS

Four 100 mm VAS were used for the four questions about the "prevalence of bruxism", "pain in the jaws", "ability to chew" and "ability to talk" during the preceding week on visits 1 to 4. The horizontal distance from the left-hand anchor to the nearest mm of the marking was rated so that higher values indicated more problems.

GOHAI

A Swedish version of the General Oral Health Assessment Index (GOHAI) with acceptable reliability and validity was used to measure general oral health. Twelve items assess three hypothesized dimensions; physical function, psycho-social function, pain and discomfort. The questionnaire was scored on a scale with five response categories (always, often, sometimes, seldom, and never). Items 3, 5 and 7 had to be reversed. The scale ranges from 12 to 60 and a high score indicates a good level of satisfaction with oral health status (219).

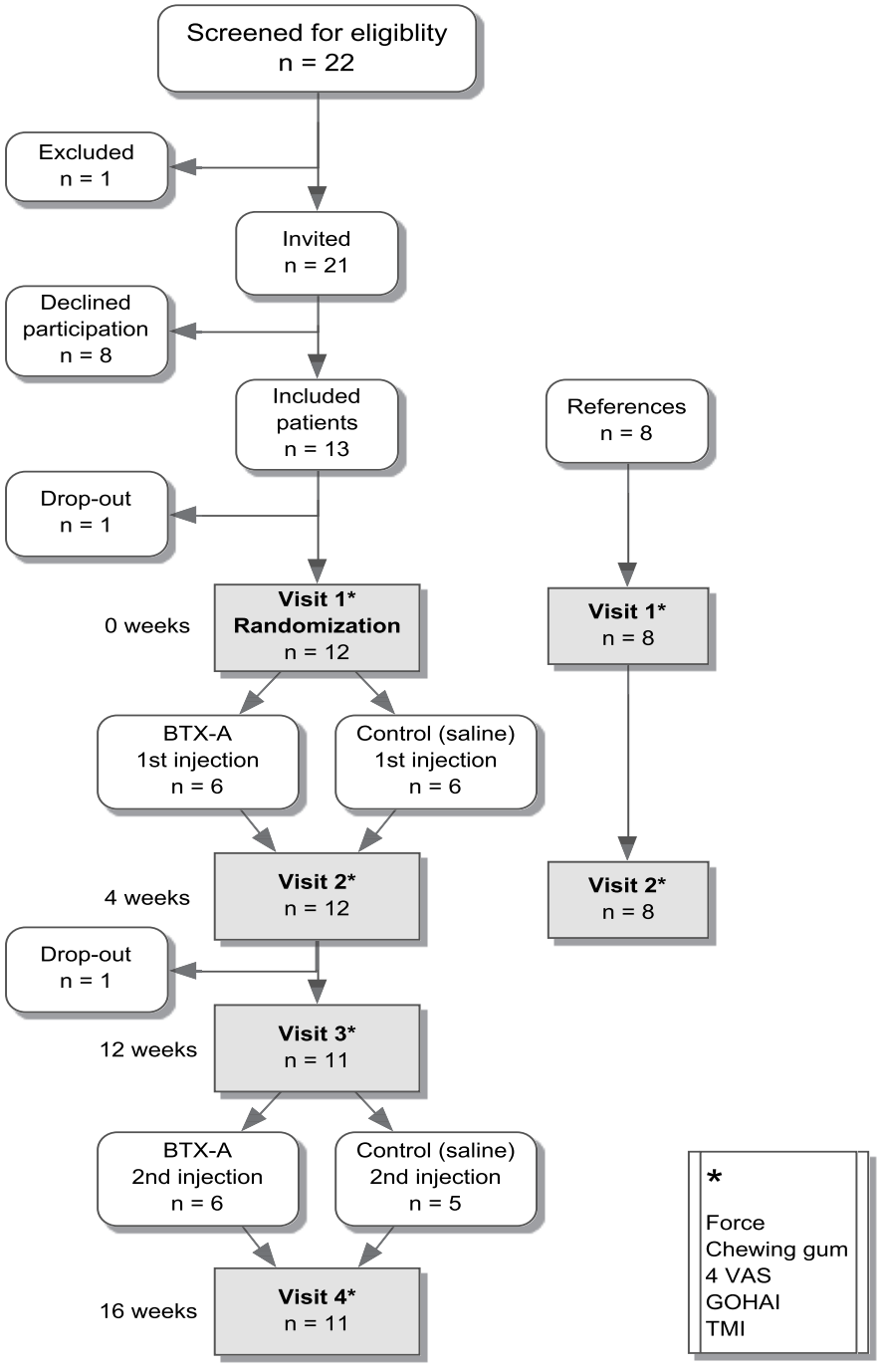

Figure 12. Flow protocol for the assignment of recruited participants to study groups and procedures in Study IV.

3.5 Statistics

Statistical tests were performed using a significance level of $P \leq 0.05$ (two-tailed), unless otherwise stated. The SAS version 9.4 statistical program was used for analyses in Studies III and IV, while an earlier version was used in Study I. A statistical program developed at Public Health and Community Medicine was used in the statistical analysis in Study II.

Study I

The distribution of differences in the use of pharmaceuticals between patients and matched controls was found to be symmetrical and was tested with Student's *t*-test and Sign test. The non-parametric Sign test was used for calculations of the differences in the distribution of the most frequently used pharmaceuticals (ATC categories) in the main diagnostic groups (RDC/TMD) for patients and matched controls.

Study II

The results were analyzed in an intention-to-treat manner for a robust interpretation. A parametric *t*-test was used to evaluate the differences between glucosamine sulfate and placebo at T0 and T1 but also over time from T0 to T1 for both groups in terms of opening capacity. Pain intensity on the VAS and VRS was calculated with non-parametric methods, Wilcoxon's signed rank test within groups and the Mann-Whitney U-test for comparisons between groups. Correlations between the VAS and VRS were performed with the non-parametric Spearman correlation test. The two dentists' inter-rater reliability and intra-rater reliability were evaluated using parametric Pearson correlation coefficients.

Study III

Statistical analyses were performed per protocol and also, for the main variables, according to intention to treat (last observation carried forward). Period-adjusted *P*-values were calculated, using the non-parametric Mann-Whitney U-test to test differences between conditions for the 13 subjects who completed the protocol. Parametric paired *t*-tests were used to test differences between conditions for the 18 subjects who participated in the baseline registration. The non-parametric Spearman's rank correlation coefficients were used to evaluate correlations between iron- and bruxism variables at baseline. For differences between drop-outs the Mann-Whitney U-test was used for continuous variables.

Study IV

Non-parametric statistical analyses were performed per protocol. A Mann-Whitney U-test was used for comparisons between patients and references for continuous variables and Fisher's exact test was used to calculate the relationship between dichotomous variables. Wilcoxon's signed rank test was used for comparisons within groups over time. Spearman's rank correlation coefficients were also used for associations between objective and subjective variables at baseline within both patients and references.

3.6 Legal and ethical aspects

In all studies (I-IV), the participants signed a consent form after receiving detailed verbal and written information about the trial.

All protocols were approved by the Regional Ethical Review Board, University of Gothenburg, Göteborg, Sweden, I (dnr S468-02), II (dnr 225-05), III (dnr 451-10) and IV (dnr 870-12) respectively, and were approved by the Swedish Medical Products Agency, II (dnr 159:2006/11407), III (dnr 151:2010/65574) and IV (dnr 15:2012/121788) respectively.

In Study I, the ethical considerations were limited, since information about medication is a normal part of the anamnesis. Medications were always given in accordance with the manufacturers' recommendations in all studies. In Study II, all the participants were provided with rescue medicine to use in case of pain. Opaque code envelopes were available in the event of undesirable reactions. In Study III, a study nurse monitored all the participants with weekly telephone calls during the forced titration procedure. A medical doctor used the clinical information for dose adjustment if needed. Vital signs and standard blood sampling for clinical chemistry and hematology were performed before and after the medication in order to document the health status of the participants. The inclusion criteria in Study IV included an ability to make independent decisions and communicate, which were considered important for ethical reasons. A medical doctor with all the necessary data available performed all the injections. All the patients made a control visit four weeks after injections. The participants were also invited to call the responsible investigator at any time if necessary.

4 RESULTS

4.1 Study I: Utilization of pharmaceuticals

Of all 600 participants included in the study, 76% were women and 24% men. Many patients at the orofacial pain clinic had more than one diagnosis according to RDC/TMD, but, with respect to the main diagnosis, a muscle disorder (RDC/TMD I) was the most common in 44%. A main diagnosis of disc disorder (RDC/TMD II) was met for 39% and for joint disorder (hard tissue) (RDC/TMD III) for 17%.

TMD patients used pharmaceuticals significantly more often than controls. More than half the TMD patients used some medication on a regular basis compared with 36% of the controls ($P < 0.001$). Reported drugs (ATC categories) used regularly by the TMD patients were a mean of 0.9 (SD 1.2) and among controls 0.5 (SD 0.9) ($P < 0.001$).

In RDC/TMD I, II and III, female TMD patients used drugs from 48, 26 and 34 different ATC categories respectively, while male patients used them from 21, eight and seven categories respectively. The most frequently used medications (ATC categories) among all female and male TMD patients and controls are given in percent in *Table 4* regardless of diagnostic group.

Female patients used medication significantly more often compared with controls in the diagnostic group RDC/TMD I for tranquilizers (N05B) ($P < 0.05$), sleep medication or sedatives (N05C) ($P < 0.05$) and antidepressants (N06A) ($P < 0.001$). Moreover, female patients, diagnosed in RDC/TMD III, used antidepressants (N06A) significantly more frequently than controls ($P < 0.01$). No other significant differences were seen between patients with specific diagnoses and controls, either for women or for men.

Table 4. The most frequently used medications (ATC categories) in percent.

Patients				Controls			
Women n = 229		Men n = 71		Women n = 229		Men n = 71	
G03A contraceptive	17	N06A antidepressant	10	G03A contraceptive	11	C07A beta recept. block.	12
N06A antidepressant	17	C07A beta recept. block.	6	H03A thyroid hormone	6	B01A anti-coagulant	7
M01A NSAID	6	M01A NSAID	6	C07A beta recept. block.	5	A10A insulin	4
H03A thyroid hormone	5	N02A opioid	6				
		N05B ataractic	6				
		N05C sedative	6				
		H03A thyroid hormone	4				

4.2 Study II: Glucosamine sulfate

Fifty-nine referrals, 51 women, and eight men, mean age of 60 ± 13 years and 57 ± 11 years respectively, with degenerative TMJ changes, a diagnosis of RDC/TMD IIIb, confirmed radiographically, were included. Most of them had a symptom duration longer than 24 months. Forty-nine completed the study. Drop-outs were seen both from the glucosamine and the placebo groups and mainly caused by gastrointestinal side-effects also in the placebo group. One-third of all participants in the glucosamine group and almost 10% in the placebo group reported gastrointestinal reactions. All side-effects were mild and had resolved after the end of the study. Rescue tablets were used by 45% in the glucosamine group and 78% in the placebo group among the patients who completed the trial.

At baseline (T0) the groups were similar in all variables, apart from significantly better mouth-opening capacity without pain in the placebo group. After six weeks of intervention, statistically significant improvements over time from T0 to T1 were registered for all four outcome variables in the glucosamine group but only for the VRS in the placebo group. No significant difference was found in any outcome variable between the groups after six weeks of treatment (T1) (*Table 5)*. The mean difference and CI between the

glucosamine and control arms in change over time on the VAS was 3.7 (95% CI -8.2 to 15.7), on the VRS 0.2 (95% CI -0.5 to 0.9), on opening without pain -1.7 (95% CI -5.1 to 1.6) and on opening with pain -1.2 (95% CI -3.1 to 0.7).

The VAS and VRS correlated significantly at T0 and at T1 (n = 59; $r_s = 0.89$ and $r_s = 0.87$ respectively; $P < 0.0001$).

Table 5. Mean (SD) of VAS, VRS, opening capacity without and with pain in glucosamine (n = 30) and placebo (n = 29) groups at baseline, T0, and after six weeks of treatment, T1, analyzed according to intention- to- treat with p values for the differences between groups and over time.

Variable	*Treatment group*	*T0*	*T1*	*P value*
Pain on VAS 0-100 mm	Glucosamine	48.1 (25.8)	38.7 (28.8)	≤ 0.05
	Placebo	42.5 (27.8)	36.8 (20.8)	N.S
P value		N.S.	N.S.	
Pain on VRS 0-6	Glucosamine	3.2 (1.3)	2.5 (1.6)	≤ 0.01
	Placebo	2.8 (1.4)	2.2 (1.2)	≤ 0.05
P value		N.S.	N.S.	
Opening wo pain (mm)	Glucosamine	32.1 (8.9)	34.7 (10.3)	≤ 0.05
	Placebo	36.5 (7.9)	37.3 (6.3)	N.S.
P value		≤ 0.05	N.S.	
Opening with pain (mm)	Glucosamine	41.3 (6.9)	42.5 (6.8)	≤ 0.05
	Placebo	42.2 (6.5)	42.2 (6.2)	N.S.
P value		N.S.	N.S.	

Number needed to treat (NNT) was calculated to 4.01.

A subgroup analysis split VAS ratings into high and low at T0 was made. The improvement in self-rated pain on the VAS from T0 to T1 was significantly better in the high rating subgroup (initial VAS > 39 mm) than for those in the low rating subgroup for both treatment arms. No difference between subgroups could be detected with similar analyses of improvements in self-rated pain depending on symptom duration (more or less than 24 months), age (more or less than 60 years), or uni- or bilateral radiographic TMJ changes.

4.3 Study III: Pramipexole

Twenty subjects, 12 men and eight women, middle-aged and slightly overweight but otherwise healthy, were included in the study. The percentage of drop-outs in the study was, 35%, but there was no significant difference between drop-outs and those completing the study in terms of bruxism episodes/h at baseline. For the 13 participants who completed the study, the PSG diagnostic criteria for SB according to Lavigne *et al*. were fulfilled (total episodes/h, mean 11.3 (6.3)) and nine of the subjects fulfilled at least one of the RDC/TMD diagnoses at baseline. Seven had myofascial pain, four had disc displacement with reduction and two had arthralgia. No statistically significant difference was seen in TMI mean between baseline, PPX and CTR conditions; 0.17 (0.12), 0.13 (0.10) and 0.12 (0.10) respectively.

Sleep fragmentation was observed after PPX treatment with a higher number of awakenings ($P = 0.03$) and a higher percentage of awake time after sleep onset ($P = 0.02$) compared with CTR. REM sleep decreased ($P = 0.02$) after PPX treatment and a small reduction in the total AHI ($P = 0.05$) was associated with PPX.

The numbers of bruxism bursts and episodes (total, phasic, tonic and mixed) remained unchanged after PPX treatment (total episodes/h 12.7 (8.5) and 9.8 (5.2) during PPX and CTR conditions respectively). Individual results for the main variable, total episodes/h, are given in *Figure 13,* at baseline, PPX and CTR. The differences, analyzed with a parametric method, between the PPX and CTR conditions were not statistically significant with respect to the number of bruxism bursts/h ($P = 0.09$), total episodes/h ($P = 0.19$), phasic episodes/h ($P = 0.09$), tonic episodes/h ($P = 0.77$) or mixed episodes/h ($P = 0.12$). Bruxism episodes were associated with arousals in more than 90% in all of the three registrations.

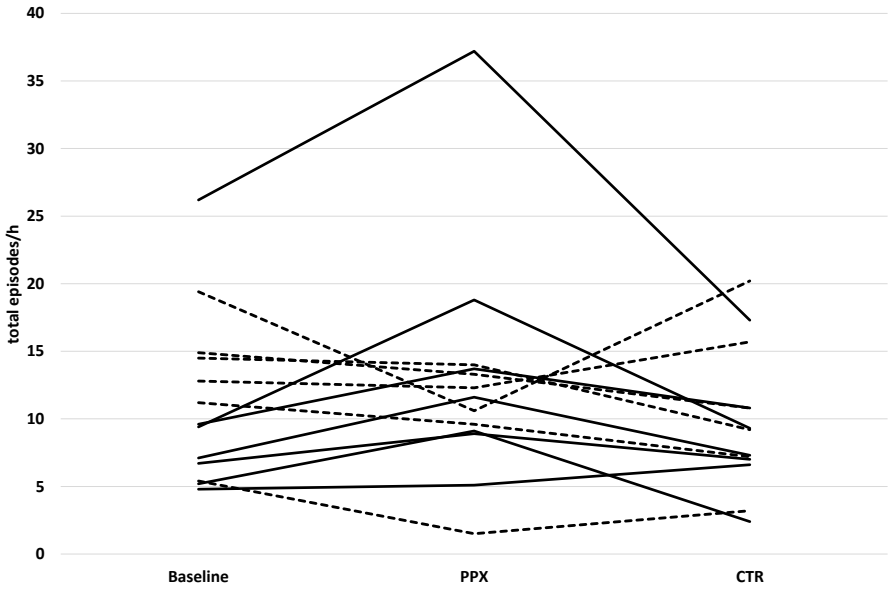

Figure 13. Individual total episodes/h of bruxism at baseline, after PPX, and after CTR for the 13 participants who completed the study (increased ——— respectively decreased ----------).

No statistically significant difference between iron-related biomarkers and bruxism variables was seen at baseline, but trends toward negative associations could be distinguished between serum ferritin and bruxism bursts/h, r_s - 0.46 ($P = 0.06$), total episodes/h, r_s - 0.41 ($P = 0.09$) and phasic episodes/h, r_s - 0.41 ($P = 0.08$).

Only three of 13 participants had an incidence of periodic limb movements at baseline. There were no treatment-related significant differences in any of the sleepiness or quality of sleep data evaluated by the IRLSS, ESS, FOSQ, ISI, KSS PSQI and MOS questionnaires or quality-of-life data obtained from the SF-36 questionnaire.

Reported adverse effects were mild and transient and did not lead to any dose adjustment or termination of medication. No changes in routine clinical chemistry were seen.

4.4 Study IV: Botulinum toxin-A

Eleven patients (5 women, 6 men) of twelve and eight references (2 women, 6 men) completed the study. One patient reported side-effects ("restless and tensed") after the first injection (saline) and dropped out after visit 2.

Anthropometric and dental data showed that both groups were middle-aged on average, with full dental arches and good dental occlusion. RDC/TMD diagnoses Ia and Ib were more common and dental attrition was more pronounced among patients, compared with matched references. The eight matched references were stronger, chewed more efficiently and rated themselves as healthier for all variables on average compared with the first eight registered patients on visit 1. Statistically significant differences were shown for five of ten outcome variables. References were stronger in finger-thumb force, they chewed more efficiently (chewing-gum), rated themselves as better for "ability to chew" (VAS), were more satisfied with their oral health status (GOHAI) and had fewer signs and symptoms of temporomandibular disorders (TMI).

An analysis of the correlations between objective variables (three force measurements, chewing efficiency and TMI) and subjective variables (four VASs and GOHAI) in the first eight patients and among the matched references on the first visit was made. Among patients, good chewing efficiency was correlated with high self-rated "pain in the jaws" (r_s 0.88, P = 0.05), with low self-rated "ability to chew" (r_s 0.97, P = 0.01) and with low self-rated oral health (r_s -0.95, P = 0.01). These three correlations among patients differed statistically significantly from the corresponding correlations among the references (all P = 0.01). Among references, high self-rated "pain in the jaws" was correlated with low chewing efficiency (r_s -0.75, P = 0.03) and with high bite force "as when chewing" (r_s 0.70, P = 0.05).

All outcome variables were analyzed on visit 4, after 16 weeks, after two injections with BTX-A or saline. Maximum voluntary contraction (MVC*)* and chewing force "as when chewing" declined substantially at group level (45% and 30% respectively) in the active treatment arm, but the reduction did not differ statistically significantly from that in the control arm. The results showed no statistically significant differences between BTX-A and controls for any outcome variables except for "ability to chew" on the VAS, which was significantly better in the active arm on visit 2. The changes from visit 1 to visit 4 did not differ statistically significantly between patients who received BTX-A or saline injections respectively, for any outcome variables.

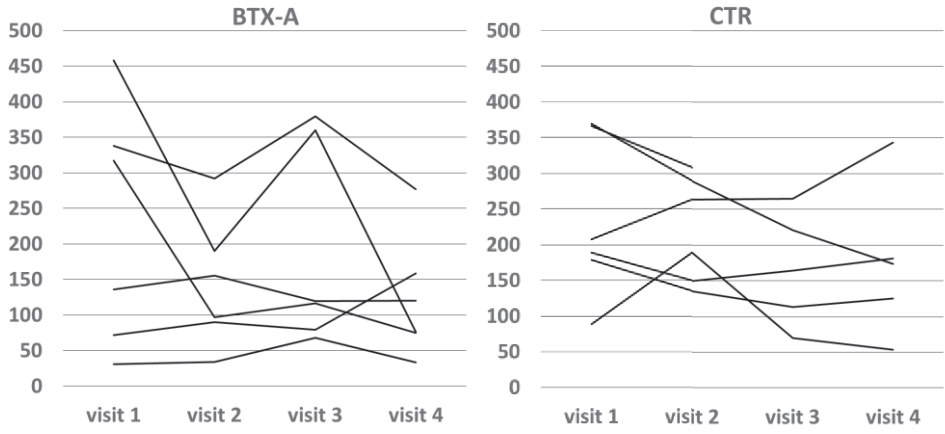

Figure 14. Individual data on MVC (N), at all visits for the 12 patients with BTX-A or CTR (saline) injections respectively.

If a decrease in MVC of 30% or more is regarded as a successful treatment, two patients from the active arm and two from the control arm were responders. On an individual basis, it should be noted that three patients with an MVC similar to that of references experienced a greater benefit from BTX-A. They all showed a reduction in MVC on visits 2 and 4 *(Figure 14*.). If a 30% or more improvement in GOHAI is regarded as successful treatment, there was one responder in the BTX-A group and two in the control group.

Nearly all (10/11) patients were positive about coming for an extra visit, three months after the last injection, for a BTX-A injection. After this, 64% of all patients wanted to continue with BTX-A on a regular basis.

BTX-A was well tolerated by the patients and no adverse events were reported, apart from one patient in the CTR group.

5 DISCUSSION

TMDs and SB are two common conditions which can cause considerable problems and significant distress. This thesis emerged from a number of somewhat different questions in clinical practice at an orofacial pain clinic and represents pieces of work designed to extend our knowledge of medication in TMDs and bruxism. The aim was to explore aspects of pharmaceutical intervention in TMDs and bruxism. The regular use of medications among TMD patients was registered to elucidate their general health condition. The effects of some putative pharmacological therapies for osteoarthritis and bruxism on pain, dysfunction and undesirable orofacial activities, as well as adverse effects, were also critically assessed.

5. 1 Study I: Utilization of pharmaceuticals

The main finding in this study was that women with a TMD diagnosis of masticatory muscle pain according to RDC/TMD axis I used significantly more antidepressants as well as tranquilizers, sedatives and sleep medication compared with controls. Female patients, diagnosed with a disorder of the bony component of the joint, also used antidepressants significantly more frequently than controls.

There is a well-known connection between depression, anxiety, stress and TMDs, based on both questionnaires and experimental methods (37, 220). Perceived stress and negative mood predicted two to threefold increases in new-onset TMDs investigated with psychologic questionnaires (36). Pain can also be exacerbated by sleep disturbances (6) and TMD patients with poor sleep report significantly higher scores for perceived pain severity and psychologic distress than good sleepers (138). These results were confirmed in our study by investigating the regular use of medication in general among TMD patients at an orofacial pain clinic and comparing it with matched controls, regular dental patients, from the same geographic area. To our knowledge, there is no previous study that shows the relationship between, on the one hand, depression, anxiety, stress and sleep problems and TMD muscle pain, on the other hand, by registering of regular medication among TMD patients compared with controls. In all probability, there is a better chance of obtaining accurate information about the daily utilization of pharmaceuticals among patients, if they are asked about medication instead of diseases. Patients may neglect to report disorders or they may feel healthy and do not wish to provide information about it or simply forget to report it during standard history taking. Communicating the use of daily medication appears to be less charged.

Patients with muscular diagnoses have previously been found to have greater problems with depression than those with articular diagnoses as judged psychometrically (221) when differentiated with RDC/TMD (222). Patients with masticatory muscle pain also appear to have more sleep problems and poorer sleep-quality but also higher levels of psychologic distress than those with intracapsular problems evaluated with questionnaires (223). In disc-related disorders, we did not observe any significant difference in the use of medications between patients and controls suggesting a different etiology compared with patients with myofascial pain. The relationship between depression and myofascial pain is controversial, but depression could probably be a risk factor for the development of certain TMDs and may also occur as a result of it. The relationship might therefore be bi-directional. In some studies, positive effects with amitriptyline, a tricyclic antidepressant, have been seen and a low dose is recommended for analgesic effect in patients with chronic TMD pain (77, 78). Depression is overrepresented among TMD patients (34, 224). The patients in this study denied using antidepressants prescribed as medication for TMDs at the history taking. The primary reason for prescriptions was probably depression. So, if depression accompanies pain, patients may benefit from supporting antidepressants, but in adequate doses to treat depression.

Tranquilizers and sedative medication were also overrepresented among female patients with muscular problems compared with controls in our study. It is concluded that psychologic factors such as stress and anxiety diagnosed by both experimental methods (38) and psychometrics (37) are common in certain subgroups of TMDs and support our findings. In the literature, there are both negative and positive reports relating to the use of benzodiazepines for pain improvement in TMDs (7, 67). The results are contradictory with respect to pain, but benzodiazepines can be used to improve sleep quality (7). Drugs for chronic pain are often administered for prolonged periods and care must be taken about the risk of abuse and the development of dependence, as well as the possibility of inducing or exacerbating depression (70).

More patients than controls used sleep medication and this applied particularly to women with masticatory muscle pain. There is also support for this association in the literature. However, the relationship between sleep disturbances and TMDs is not fully understood. Pain and TMDs are associated with poor sleep quality related to psychosocial distress (i.e. depression and/or anxiety) (225) and the frequent use of sleep medication is described in TMD patients because of poor sleep (138). A vicious cycle may be established in which the pain exacerbates the sleep problems and sleep problems in turn aggravate the pain.

It is known that patients with TMDs have impaired health (226) and use the health-care service more often than controls (227). This is also in line with the results of our study where pharmaceuticals were used significantly more frequently by patients than by controls. Perhaps the patient group has a more pronounced sensitivity to TMD pain, depression, anxiety, stress and perhaps disturbed sleep than the controls. The evidence in favor of important common underlying pathophysiologic processes is growing (228), but the question is still unresolved.

We did not find any significant differences in the utilization of hormonal replacement therapies between female patients and controls. This is supported by some earlier findings (229) suggesting that estrogen replacement therapies were not associated with any increase in the prevalence of TMDs, but contrasting with others who concluded that there is a relationship between female external hormonal factors and orofacial pain (230, 231). Nor did the use of oral contraceptives differ significantly between the groups in our study, which is also a controversial finding (231, 232). However, there was a tendency towards a difference in their use ($P < 0.10$) among women diagnosed with disc-related disorders. An association between the use of oral contraceptives and TMDs has been suggested, with an increased risk of approximately 20% (230). Even if our study was unable to reveal significant association between TMDs and sex hormone treatment, it has been argued that sex hormones influence TMDs both via peripheral joint mechanisms and via central pain-related mechanisms (233).

Limitations and strengths

We included 300 patients and 300 controls, but the smallest groups with the infrequently used drugs were still too small to find any differences with acceptable power. We could perhaps have demonstrated even more significant relationships between orofacial pain conditions and different pharmacologicals if the sample size had been accurate for the smallest group. There is a risk of type II error, false negative.

One methodological limitation is that no clinical examinations were performed in the control group, but everyone had to deny any subjective symptoms of TMDs when questioned for inclusion.

One strength is that all the participants came from the same community and were matched according to age and gender and registered in parallel as the prescription of pharmaceuticals can vary over time and region. The compliance was perfect and none of the patients or controls refused to participate in the study.

5.2 Study II: Glucosamine sulfate

Both objective (mouth opening) and subjective (pain) outcome measurements improved significantly over time among the patients in the glucosamine group in this study. The difference in change over time between the active and control arms was not significant for any outcome variable, however. In conclusion, we did not find any effect of glucosamine sulfate on osteoarthritis in the TMJ in our study. This result is supported by Wandel *et al* in a meta-analysis from 2010 concluding that glucosamine does not reduce joint pain due to osteoarthritis in the hip or knee (116). Nor is glucosamine recommended for the non-surgical management of knee osteoarthritis in recently published guidelines (117). However, there are also some positive studies in favor of glucosamine in TMJ OA (234). Another study mentioned that there might be an industry bias explaining the heterogeneity in some of the conducted trials (235). Our study was not sponsored by the pharmaceutical industry and we did not use any industry-supplied drug. Among studies with the involvement of the manufacturers, the results are often described as superior for glucosamine (235).

The study population was well defined and carefully diagnosed. Of a large number of referrals within a time period of almost four years, 59 patients were finally included. They all fulfilled the RDC/TMD criteria for OA (IIIb) in the TMJs. All the included patients underwent a radiologic examination, most of them with tomography of the TMJs, and the X-rays were reviewed by one independent specialist dentist. Radiographic degenerative changes were found in all patients on one or both sides. The diagnosis was based on anamnestic and clinical data and the radiologic examination confirmed the diagnosis. Almost 7% of all the referrals to the clinic were diagnosed with OA in the TMJ and this is in line with earlier observations at the same clinic (59).

The degree of destruction to the condylar head, age and duration of pain were not relevant to the pain relief in our study. When split between the initial self-rated pain on the VAS, the result shows that the pain relief was greater for patients with higher initial pain in both the glucosamine group and the controls. This was a surprising finding since glucosamine is recommended for mild or moderate symptoms. Perhaps mild pain in the TMJ at the study start limited or diluted the effect of the intervention. In terms of the placebo effect in the controls, it is known that the effect can be as high as one-third to two-thirds of the response rate and most effective in cases with severe pain (236).

Glucosamine is supplied as glucosamine hydrochloride and glucosamine sulfate. In a review from 2007, Vlad *et al*. found that glucosamine hydrochloride has no effect on pain (235). More positive findings have been

observed in studies of glucosamine sulfate than those of glucosamine hydrochloride. In spite of the fact that this study assessed the effect of glucosamine sulfate, we did not find any significant differences in relation to pain or mouth-opening between the groups. A recent study of patented crystalline glucosamine sulfate at a dose of 1,500 mg once daily demonstrates superiority over both glucosamine sulfate and glucosamine hydrochloride formulations, with medium-term control of pain and a lasting impact on disease progression in patients with OA in the knees (237).

Glucosamine is taken as a dietary supplement and is supposed to have fewer side effects than NSAIDs, for example. If effective, glucosamine could be an attractive alternative medication. There were some adverse events and premature withdrawals in both groups but more in the active group. One-third in the active group and almost 10% in the control group reported gastrointestinal side-effects. Side-effects are usually reported as few and often mild for glucosamine, but our study indicates that there can be more side-effects than previously reported for the drug. Possibly some of the patients with gastrointestinal side-effects suspected that they had been allocated to active treatment and this may have influenced their responses relating to self-reported pain, regardless of whether they were medicated with glucosamine or placebo. Almost half the patients who completed the trial in the glucosamine group used rescue tablets compared with 78% in the placebo group. This indicates that the active medication, glucosamine, was not good enough for pain relief but still produced a not inconsiderable quantity of side-effects.

Limitations and strengths

The manufacturer recommends at least four weeks with therapeutic doses of 1,200 mg/d glucosamine sulfate for relevant pain relief. To achieve a satisfactory pain relief effect, all subjects were treated for six weeks. Although the treatment was extended over six weeks, the study must be seen as a short-term study, which is a weakness.

One strength is that the two examiners were calibrated when measuring mandibular movements before the study and both intra- and inter-rater reliability were excellent.

Another important strength was that this study was not promoted by the pharmaceutical industry.

It took a long time to include all the patients in the study since we followed rigorous inclusion criteria. Because of this, the original expiration date for the active substance and placebo was exceeded and the last of the 60 sets of

containers were sent to the pharmacist for a quality control assay, which further delayed the study.

5.3 Study III: Pramipexole

This exploratory study evaluated the potential involvement of a dopamine-related dysfunction in SB. No systematic effect on objectively assessed SB or the symptoms thereof could be revealed after three weeks of medication with the dopamine agonist PPX.

However, it seems that the dopaminergic medication caused a slight decrease in sleep-disordered breathing as well as in the amount of REM sleep. The nocturnal awakenings were more frequent, as well as the awake time after sleep onset. Most healthy individuals with SB have a normal sleep organization and macrostructure (136, 137), but a slight increase in sleep fragmentation may have caused the small reduction in AHI.

The study population was slightly overweight and there is a known comorbidity between BMI and AHI (238).

We noted a trend towards a negative association between bruxism intensity and ferritin, an iron-related biomarker, *i.e.* high values for certain bruxism variables and low serum ferritin. Many studies have linked RLS/WED to deficiencies of dopamine and iron and many patients with RLS/WED are therefore supplemented. To our knowledge, an association between iron metabolism and SB is previously unknown.

The etiology of primary SB is not fully understood, but a dysfunction of central dopamine mechanisms has been proposed (239). SB is probably not a disorder with a single phenotype and there are most likely multiple pathophysiologic traits. SB bears several similarities to RLS/WED, a disease characterized by involuntary, semi-rhythmic periodic limb movements (PLM) during sleep (127). A common underlying neurophysiologic mechanism in both SB and PLM has been suggested (126) and changes in central dopamine activity have been considered in both conditions. The dopamine agonist, PPX, is the treatment of choice for the symptomatic treatment of restless legs, but the possible effect in SB has been insufficiently explored. However, in our study, the effect of PPX did not affect the SB. This is in line with an earlier study with a crossover design evaluating bromocriptine (181). In a case report on pergolide, also a dopaminergic agent, effects were shown in terms of a substantial and lasting reduction in the bruxism outcome measurements (169). Many of the drugs have adverse side-effects and, because of the limited safety

margin of PPX, it is not an acceptable drug for the treatment of SB, considering its mild health impact.

A natural variability in bruxism over time is reported in the literature (9) and we therefore kept the period of intervention relatively short. Two of the three study weeks involved the up-titration of the medication. Nearly all bruxism episodes were associated with arousals or respiratory events in our study, consistent with previous findings (136, 137).

All the participants in the study underwent an orofacial examination and 69% fulfilled the criteria for one or more diagnoses according to RDC/TMD axis I. The relationship between TMD and SB is complex (50). A negative association has also been observed (48). Our results show a fairly large number of TMD diagnoses among participants with SB, probably due to the recruitment from an orofacial pain clinic and not from the general population.

The participants underwent a habituation night at home and they all fulfilled the criteria for "possible SB" at inclusion and "definite SB" according to consensus statements (8) after the PSG sleep records were analyzed. They also fulfilled the PSG diagnostic criteria for bruxism on the baseline night (136). PSG is the most reliable method for diagnosing SB, as well as other sleep disorders, but it takes a great deal of time and effort on the part of the patients. In our study, we used ambulatory PSG systems with EMG recordings but without audio-video combination. The value of audio-video recording in defining SB has recently been questioned and the diagnostic accuracy appeared to remain good without this support. However, there is a risk of overestimating SB in the absence of audio-video recordings (240).

A formal power analysis was not performed, due to a lack of previous data and the exploratory purpose. A *post-hoc* analysis, based on the actual mean difference of 2.95 (7.02) episodes/h in favor of control conditions, was made after the study end to calculate adequate power to detect possible PPX-induced changes. If 47 participants had been included, this would have resulted in a power of 0.80 at alpha 0.05 and twenty participants would have resulted in a power of 0.43 at alpha 0.05. Assuming a mean difference of 4.5 (7.02) episodes/h implies that the 20 included participants would have been enough for a power of 0.78. A mean difference of 3.5 (7.02) episodes/h would require 34 participants for a power of 0.80 at alpha 0.05.

Limitations and strengths

The study participants were recruited from a pool of orofacial pain patients and not from the general population, which might have introduced a bias with a

larger number of TMD diagnoses.Measurement bias is also possible because of the non-blinded study design.

The drop-out rate was high in the study 35%, but other authors report the same proportions of withdrawals with similar types of drug (241). An analysis of baseline data between subjects who completed all the registrations and those with early study termination did not reveal any significant differences in any variables or demographic data.

The study was underpowered. Many drop-outs resulted in an inadequate sample size. It is difficult to know whether a small sample size could represent the target population and there is a risk of type II error, false negative.

In any case, one strength of the study is its clinically well-characterized study population and good study methodology for assessing SB, as well as the effects of the dopamine agonist, PPX.

We had no audio/video recordings in the ambulatory home monitoring equipment. The diagnostic accuracy of assessing RMMA with portable PSG systems appears to be good and their use is supported for both research and clinical use (240). Without audio/video recordings, it can be difficult to distinguish RMMA from other specific sleep-related movement disorders, such as coughing and sleep-talking, and an overestimation of RMMA frequency has been described (240), but an experienced certified PSG technician, blinded to the study allocation, scored all the PSG recordings according to the AASM manual (153).

5.4 Study IV: Botulinum toxin-A

In this study, BTX-A injections were given to treat masticatory muscle hyperactivity/bruxism in persons with CP. No significant differences in change over time in any variables could be seen between the BTX-A group and controls at the study end. On an individual level, some patients responded to BTX-A as expected according to MVC but the outcome could not be predicted from gender or age. The healthy matched references had a stronger, more efficient masticatory function than the patients.

There was an obvious variability in all outcome variables, both between patients but also according to the patients' own opinion over time. The range and standard deviations were large at all registrations. These factors can partially explain the lack of significant differences between patients and controls over time. Patients with CP had an inferior oral ability compared with

the healthy reference group. It is both notable and interesting that, a considerable difference was registered between patients' interpretation and the objective measurements. Patients were often satisfied, despite an objective reduced ability. Despite no improvements over time at group level, 64% of patients chose to continue with BTX-A after they had tried it at an extra last visit. The interpretation is that the patients thought they experienced some benefit from the BTX-A.

Since no effective treatment for TMDs or the protection of dental structures can be offered to patients with "special needs" and neuromotor disturbances in the masticatory muscles, it is important to investigate possible alleviating methods, such as BTX-A injections. BTX-A injections to treat spasticity in other muscles in CP patients are common and guidelines for the therapy of arms and legs have been drawn up (242).

Bruxism is strongly associated with a negative impact on quality of life in children with CP (243). It would therefore be useful to find effective help by listening to the patients' own opinion. If we had found a positive result for the CP patients, the expectation was that the results could be generalized to other populations of "special needs" as well.

All CP patients were 18 years or older and they all had reported bruxism and were able to make decisions and communicate with varying levels of ability. Some also had difficulty with speech, chewing and swallowing. About half the patients had a normal MVC, while others had weak masticatory muscles at the start. It appears that the variability in muscle strength in CP patients is greater than in an ordinary population. A wide range necessitates a larger sample size for adequate analyses. MVC are supposed to vary between visits for a healthy population and probably even more for CP patients. It is also likely that CP patients are more sensitive to external influences and the variability appears to vary from one day to another in terms of emotional state, infections, fatigue and so on. Even the time of day can make a difference. They can also be affected by their medication or epileptic seizures.

It is not known to us which type of CP the patients had, since no medical examination or medical record check-up was made before the trial. There was also a large variation in the patients' disability level, varying from mild (walk) to severe (unable to walk).

The purpose of the BTX-A injections bilaterally in the masseter and temporalis muscles was to act on the entire masticatory system. In this study, a total of 100 units were distributed with 30 units in the masseter muscles and 20 units in the temporal muscles on each side. In the literature, using a total of 150 units

is also common (100). It is worth considering whether this amount was less effective than a higher dose. The saline injections were thought to act as a placebo, but it is known that there can be a "needle effect" (244).

The intention was to investigate the effect of BTX-A and no further therapeutic arrangement was made. The effect might be increased and the sustainability improved if physiotherapy had, for example, been included in both groups (245).

All the outcome variables except one were similar over time in the reference group. This indicates that the methods were reliable, at least for a healthy population.

Limitations and strengths

A power calculation was made before the study start based on an earlier study of bite force reduction after injections with BTX-A. This showed a need for a total of 16 study participants for a significant effect (92). Even though we included patients for a long period, we were not able to include this number of participants. Because of difficulties enrolling patients in the region, the study was terminated prematurely. A *post-hoc* power analysis of the patients' maximum voluntary muscle contraction changes from visit 1 to visit 4 was only revealed in a power of 0.14. To reach a power of 0.80, there had to be 75 patients in each of the two groups. Depending on the small sample size, there is an obvious risk of a type II error, false negative. A multicenter study to ensure adequate sample size should be advocated.

Another consideration is the difficulty involved in duplicating the placement of the bite fork for measurements of the bite force. A rubber tube on the bite fork was carefully marked to allow duplicate placement, distal to the right canine, but, because of the spasticity, this was difficult to implement in some cases.

5.5 General discussion

Impaired general health is a risk factor for TMD symptoms and reported bruxism (226). Quality of life can be significantly affected by the influence of both TMDs and SB. TMD patients use the health-care service as well as sick leave more frequently (227) and prescribed medications can reflect the health of the patients. There is evidence of significantly more utilization of medication by TMD patients compared with healthy controls. A connection between TMDs and depression, anxiety, perceived stress and sleep disturbances is known, as well as a comorbidity between TMD patients and

those seeking care for other somatic pain conditions, such as fibromyalgia and whiplash.

Pharmacologic therapies in TMD treatment are used not only to manage acute pain and anxiety but also to control long-lasting local and systemic disease. Moreover, by studying medications, hypotheses about the etiology and mechanisms of the conditions can be elucidated for both TMDs and bruxism. If patients respond to a certain medication, this might assist in establishing a diagnosis. An appropriate drug must be selected based on the specific etiology. TMDs may be of a primarily psychosocial nature or pathophysiologic origin, *e.g.* inflammation or trauma. The medication needs to be adapted to the etiology of the pain. No single drug known today is able to treat the full range of causal factors in TMDs. The relationship between TMDs and bruxism (awake bruxism and SB) is complex and there is still no conclusion about whether or not there is an association (49, 50). However, similar types of pharmaceuticals, such as benzodiazepines, antidepressants and BTX-A, have been tested for both TMDs and bruxism. For the management of SB, no definitive pharmacologic therapy can be recommended today, but there is hope for tomorrow, if we can learn to understand the etiology. More controlled, evidence based research is needed to find a potential etiology-based cure. Medications are therefore important, not only for treatment but also to elucidate background factors, comorbidity and mechanisms in TMDs and bruxism.

Many drugs for treatment of TMDs and bruxism have been proposed, examined and rejected over time. Some medications were ineffective for the purpose, but one common reason for discarding a treatment is an unacceptable safety margin. If the disorder only has a limited impact on health, the benefit of medication should be carefully considered because of the risk of serious side-effects. The benefit must be greater than the harm. However, although it was not possible to demonstrate a superior effect over placebo for the investigated drugs in these studies, there are other proposed medications for pain and bruxism relief with varying degrees of side-effects. Hippocrates' advice to everyone engaged in the art of healing, is still valid and important to remember:"Primum non nocerum. (First do no harm)".

6 CONCLUSIONS

Study I

The use of pharmaceuticals differs between temporomandibular disorder patients and controls from the same community. The average number of reported drugs was almost twice as high in the group of patients with temporomandibular disorders compared to controls. Female patients with a diagnosis of muscular or joint origin used antidepressant drugs significantly more than controls. Female patients with muscle disorders also used tranquilizers, sleep medication or sedatives significantly more than regular dental patients.

Study II

Glucosamine sulfate was not superior to placebo in reducing the signs and symptoms of osteoarthritis in the temporomandibular joints at group level.

Study III

The involvement of the dopamine system in bruxism is less likely and the administration of the dopamine agonist, pramipexole, did not reduce the severity of sleep bruxism in patients with an established sleep bruxism disorder, confirmed by polysomnography/electromyography monitoring.

Study IV

No significant differences between botulinumtoxine-A and control injections in the masticatory muscles, for either subjective or objective variables, could be observed at group level. The group of patients with cerebral palsy and bruxism was very heterogeneous and the subjects' oral capabilities also varied greatly over time. However, there are perhaps more benefits than drawbacks when it comes to botulinumtoxine-A injections for the temporary treatment of bruxism in cerebral palsy patients, since the majority of patients in both groups asked to continue active treatment.

7 FUTURE PERSPECTIVES

Due to the curiosity that has grown over the years, this thesis reflects different aspects of interest in the area of orofacial pain, bruxism and medication. Finally it has been possible to link this work together and compile it in this thesis. Within each area of interest, several new questions that need to be answered have emerged. Study materials that have not as yet been analyzed or included in this work have also been collected. It is therefore with great confidence and joy that I plan to proceed with research.

A further study of BTX-A injections in the masticatory muscles with a view to reducing bruxism needs to be performed, since the present results are inconclusive and BTX-A appears to be both safe and well tolerated. The included participants need to have a bite force of more than 200–250 N, or alternatively, the participants can be stratified in more homogeneous bite-force groups. A multicenter study with larger, more homogeneous groups of participants with "special needs" and severe bruxism would be desirable. Another interesting area of research is a possible association between iron metabolism and SB. There is a known overrepresentation of iron-deficiency anemia in RLS/WED and a similar neurophysiologic mechanism in both SB and PLM is suggested. For this purpose, a study with interdisciplinary collaboration between dentistry and medicine would be warranted. Another useful evaluation, if it is possible, would be to analyze PSG/EMG base line data to predict whether a patient will respond to PPX treatment. Furthermore, it would be interesting to analyze our data to see whether a habituation night is necessary before measuring SB with PSG/EMG at base line conditions. Finally, new pharmacological treatments for pain are constantly being launched and indications, contraindications and side-effects need to be specifically explored in TMD patients before they can be recommended for this group of patients.

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APPENDIX

All forms are described in the thesis and can be provided by the author on request.