



## **Bioregulatory Properties of Medications Aiming at Multiple Targets Open New Therapeutic Perspectives**

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# Multitarget Regulation in Modern Bioregulatory Medicines

Alta A. Smit, MD

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In the history of modern medicine, we have been experiencing many paradigm shifts driven by advancements in scientific knowledge followed by development of new tools to finally demonstrate validity of the underlying hypotheses—the scientific evidence.

One of the shifts painstakingly taking place at the moment is the shift back from reductionist to complex thinking.

In the words of John Holland: “For the last 400 years science has advanced by reductionism. . . . The idea is that you could understand the world, all of nature, by examining smaller and smaller pieces of it. When assembled, the small pieces would explain the whole.”<sup>1</sup>

Biological systems, however, are complex with properties that cannot be explained by assembling all the pieces. They therefore pose a challenge for drug discovery and reductionist thinking, which is thought by some to have a detrimental effect on this process.<sup>2</sup>

Disease processes as well are difficult to reduce to a collection of linear events. Most malignancies are of multifactorial origin and consequently have multiple targets to be addressed when successful treatment is the goal. This also applies to the majority of diseases with immunological and inflammatory pathophysiology such as rheumatoid arthritis or possibly chronic osteoarthritis<sup>3</sup> as well as chronic diseases with hypothesized interaction between more than one organ system such as irritable bowel syndrome and inflammatory bowel disease.<sup>4</sup>

Drug combinations offer a promising strategy to address this issue, as they are generally more specific to cellular contexts than are single agents; however, the concern is that therapeutic synergy will be accompanied by synergistic side effects.<sup>5</sup> Multicomponent medications are medications that go beyond the common model of “one molecule—one target.” More specifically, a multicomponent medication is a formula consisting of more than one active ingredient that can be either molecules or herbal extracts, depending on the complexity of preparation. Examples include any herbal medication (eg, any herbal traditional Chinese medicine preparation) or Sudafed Cough&Cold. Plant materials, through their multicomponent nature and therefore combination chemistry, may be especially

well suited for such a multitarget approach.<sup>6</sup> The use of ultra low\* concentrations of substances offers another avenue for the delivery of nontoxic interventions with novel areas of application. This approach is a therapy pathway for both conventional and alternative medical therapies for reaching the right balance between clinical outcomes and side effects.<sup>7,11</sup>

Bioregulatory medicine is an emergent science concerning itself with complex bioregulatory networks, as well as using multicomponent medicines to manipulate networks and multiple organ systems rather than single targets.<sup>12</sup> In this supplement, some exemplified principles of bioregulatory medicine and its role in the multitarget approach are depicted and data from past and ongoing research are presented. To validate these concepts, however, high-quality research in this field is warranted. An interesting role may be played by bioinformatics, which lends itself to compute multiple networks and interactions.<sup>13,14</sup>

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\*The concentration of an ultra low dose differs from substance to substance. In the medications described in this supplement, it either is in the range of 1/10 of its physiological concentration in the case of a so-called metabolic factor, or in plants, it is often dictated by the toxicity of the plant and then included above the so-called first safe dilution. This is normally a 1:10 000 dilution of the plant.

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A very recent and easy to study handbook on Biopuncture can be found with the following reference: Kersschot J. *The Clinical Guide to Biopuncture: The Use of Biotherapeutic Injections in Everyday Practice*. Aartselaar, Belgium: Inspiration; 2010.

# Irritable Bowel Syndrome

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Approximately 10% to 15% of the adult population suffers from irritable bowel syndrome (IBS), although in many, the symptoms are relatively mild. However, because the condition is so common, even if only one patient in 10 consults a physician, this represents a burden on health services in excess of that posed by inflammatory bowel disease. Furthermore, although there are effective treatments for inflammatory bowel disease, such as mesalazine, steroids, azathioprine, and biological therapies, there have been no new pharmacological agents available in Europe for the treatment of IBS for more than 20 years, and there are relatively few in the pipeline.<sup>1</sup> Despite the enormous size of the IBS problem, pharmaceutical companies have been deterred from entering this field because of the complexities of the underlying pathophysiology as well as the excessive demands of the regulators in terms of safety and the lack of agreement on suitable outcome measures. It is now recognized that IBS is a multifactorial problem; therefore, concentrating on one particular mechanism is likely to help only a subset of individuals at best. In addition, targeting one specific receptor is quite a risky strategy because of the built-in redundancy of biological systems whereby if one receptor is blocked, another may take over its function. This may explain why the more old-fashioned “dirty” drugs such as tricyclic antidepressants seem to be relatively useful in IBS. It may also account for why probiotics are of benefit in IBS as they too have such a wide range of different activities.

Our understanding of the pathophysiology of IBS has advanced considerably during the last two decades.<sup>2</sup> IBS was initially thought of as just a disorder of motility, but it is now recognized to be a complex interaction of physiological and psychological phenomena on which impinge a whole host of exogenous factors such as microbes and nutrients (Table). There is also a strong familial incidence of the condition,<sup>3</sup> suggesting that genetic factors<sup>4</sup> as well as social learning are important. Thus, there is compelling evidence that IBS is multifactorial in origin.

There are currently two models for explaining disease expression: the biopsychosocial and the heterogeneity models. The former attributes disease to the interaction of physical, envi-

**TABLE** Putative Pathophysiological Mechanisms in Irritable Bowel Syndrome

Abnormal motility
Disturbed visceral sensation
Abnormal central processing of gut sensations
Inheritance
Dietary factors
Inflammation
Gut bacterial imbalance
Neuroendocrine factors
Psychological factors

ronmental, and psychological factors,<sup>5,6</sup> and the latter considers the possibility that IBS is not a single entity but a collection of disorders with different etiologies. Obviously, both of these hypotheses have major implications with respect to treatment and especially the development of new therapeutic modalities.<sup>1</sup>

With this increase in the appreciation of the diverse pathophysiology has come a greater awareness of the clinical manifestations of the disorder, such as the fact that it is just as common in the elderly<sup>7</sup> and that symptoms can be extremely severe, especially in patients referred to secondary care. Female patients liken the pain to that of childbirth,<sup>8</sup> the bloating can be accompanied by an increase in girth of up to 12 centimeters,<sup>9</sup> and the bowel dysfunction can be extreme. For instance, the diarrhea is not infrequently accompanied by fecal incontinence, and it has been shown recently that long-term constipation can be as much of a risk for pelvic floor damage as giving birth.<sup>10</sup>

Another facet of IBS is the tendency of patients to experience a variety of noncolonic symptoms such as backache, lethargy, and a range of urological as well as gynecological symptoms.<sup>11</sup> Of the latter, dyspareunia is common, and this may partly explain why so many women find that IBS interferes with sexual function.<sup>12</sup> These noncolonic symptoms are also important because they may result in general practitioners referring patients to the wrong specialty. For instance, if the back pain is prominent, it might be considered orthopedic or if the pain is worse with menstruation, which is very common in IBS, a gynecological opinion might be sought.<sup>13,14</sup> In this type of situation, patients can be subjected to a variety of inappropriate investigations or even undergo unnecessary surgical interventions. Not surprisingly, with all of these issues affecting their lives, individuals with IBS can experience an erosion of quality of life (QOL),

which may become so poor that it can be worse than that suffered by patients with end-stage renal disease or diabetes.<sup>15</sup> As a result, a sense of hopelessness can be engendered, which can lead to patients feeling suicidal,<sup>16</sup> especially in view of the notorious inadequacies of treatment and the prospect of no relief of their symptoms in the future.

The management of IBS is difficult as it involves a “trial and error” approach that often is time consuming and frustrating for both patient and physician alike. Dietary manipulation has to take into account the fact that sufferers may actually be intolerant of foods that are traditionally considered healthy. Consequently, cereals may have to be avoided because they contain insoluble fiber.<sup>17</sup> Fruits and vegetables may cause problems due to their content of fermentable oligo-, di- and monosaccharides and polyols.<sup>18</sup> The mainstay of pharmacological treatment is the use of antispasmodics in combination with antidiarrheals or laxatives as appropriate. If these fail, then antidepressants either of the tricyclic or serotonin reuptake inhibitor class can be tried; gastroenterologists favor the former,<sup>19</sup> despite trial evidence suggesting that both classes are equally effective.<sup>20</sup> Once all pharmacological approaches have been exhausted, a variety of behavioral techniques can be offered, including psychotherapy, hypnotherapy, and cognitive behavioral therapy.<sup>21</sup> In addition, it has been shown that patients with IBS are frequent users of complementary and alternative therapies<sup>22</sup> such as homeopathy.

With the possible exception of tricyclic antidepressants, the drugs that are currently at our disposal target only one of the putative pathophysiological mechanisms of IBS and therefore, for instance, antidiarrheals may improve loose bowels but do nothing for pain. Likewise, antispasmodics may improve pain but have little or no effect on bowel habit. Consequently, it may be necessary to use combinations of these medications, and even then it is difficult to address all the mechanisms involved in a particular individual. Thus a case could be made for the concept that developing a preparation with a variety of activities might have considerably more potential in the treatment of IBS than the current approach of concentrating on compounds with a narrow spectrum of activity. It is difficult to predict which would be the most rewarding combination of abnormalities to address, but based on the current state of knowledge, an effect on motility, visceral hypersensitivity, inflammation, and possibly the central nervous system (especially in cases of anxiety) would seem to be an obvious goal. However, another hurdle to testing such an approach is the problem of the design of clinical trials in this area.

In order to try to improve the quality of clinical trials in IBS, a variety of diagnostic criteria have been developed. The first is the Manning Criteria,<sup>23</sup> followed by various versions of the Rome Criteria, of which Rome III<sup>24</sup> is the most recent (although how this latest version compares with the previous ones remains to be determined). The Rome criteria are the most widely used, although the Manning Criteria still have a lot to commend them. Certainly the development of criteria has greatly improved the homogeneity of patients entering clinical trials, although they

give no indication of severity. There are only two instruments for measuring severity: the Functional Bowel Disorder Severity Index<sup>25</sup> and the IBS Symptom Severity Score.<sup>26</sup> The latter is specific for IBS, is used widely for assessing severity, and can be used as an outcome measure in terms of defining a responder as a 50% reduction in his or her score. However, this instrument has the disadvantage that a 50% reduction of a high score may not be clinically similar to a 50% reduction of a low score, although there are some data to suggest this may not be such a problem as might be expected.<sup>27</sup>

Other outcomes are designed to capture improvement in terms of whether, compared with how they were before treatment, patients consider their symptoms to be adequately or satisfactorily relieved.<sup>28</sup> The US Food and Drug Administration (FDA) has recently announced that it considers all the currently used outcome measures in IBS suboptimal. The FDA has therefore initiated a program of development of a patient reported outcome measure, although the final version will not be available for a few years. In the meantime, trials will continue to use existing outcome measures. All clinical trials in IBS should also be accompanied by a QOL assessment. A number of these are available, but the IBS QOL is probably the most widely utilized.<sup>29</sup>

The final obstacle to drug development in this field is the very strict line on safety that has been adopted by the regulatory authorities in relation to any new drugs for IBS.<sup>30</sup> This stance is based on the assumption that IBS is not a fatal condition, despite the fact that some sufferers are driven to suicide and their QOL can be poor. Regulators also fail to appreciate how desperate patients are to have some new therapeutic options for this condition. This desperation has recently been highlighted by a study showing that patients would be prepared to trade some life expectancy or risk of severe side effects from a drug in order to gain some relief from their symptoms.<sup>31</sup> At least these restrictions would not apply to bioregulatory medicines with their ultra low-dose formulations and resulting safety profile.

Thus in summary, there is a huge unmet need for new therapeutic options in IBS, but there are a number of impediments to progress in this area. These include knowing what mechanisms to target as well as trying to meet what could be considered to be the excessive needs of the regulators in terms of design of trials and especially safety.

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# ASBRM



American Society of  
BioRegulatory Medicine

## Who is ASBRM?

The American Society of BioRegulatory Medicine (ASBRM) is a scientific society formed to support education in bioregulatory medicine. We believe that a new model of health-care information and education based on an individualized, whole-systems approach is emerging. Through collaborative efforts with the other international organizations, we provide educational opportunities in a variety of topics—ranging from primary care to veterinary medicine. Our mission is to advance the recognition that all treatment must be patient centered and individualized, rather than disease centered.



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- ✓ Inclusion on a publically available, international, practitioner finder list
- ✓ Educational seminars and other scientific events and symposia
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# The Bioregulatory Approach to Work-related Musculoskeletal Disorders: Using the Multicomponent Ultra low-dose Medication Traumeel to Target the Multiple Pathophysiological Processes of the Disease

Konstantin Cesnulevicius, MD, PhD

The burden of chronic diseases in modern society is well recognized. Increasing resistance to existing drugs, a decreasing number of new effective drugs, and a growing number of comorbidities in the aging population force the medical community to look for innovative approaches in disease management. Bioregulatory medicine is one of such approaches. The multifactorial origin of many chronic diseases suggests multiple targets to be addressed when successful treatment is the goal. This also applies to most diseases with immunological and inflammatory pathophysiological features, such as work-related musculoskel-

etal disorders. Consequently, strategies for the development of either rationally designed multitargeted agents or the optimization of combining existing targeted agents are essential. Traumeel is a medication with bioregulatory properties that has been successfully applied to treat musculoskeletal injuries. This article provides an overview of current scientific evidence about this medication and proposes a hypothesis of possible mechanisms of action presented from a viewpoint of a pathophysiological model of work-related musculoskeletal disorders. (*Altern Ther Health Med.* 2011;17(2 Suppl):S8-S17.)

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**B**ioregulation is defined as the regulation of biological processes.<sup>1</sup> Bioregulatory medicine aims to target these processes in the human organism to restore proper functioning of autoregulating feedback loops that have been impaired during disease evolution. The hallmarks of bioregulatory medicine can be summarized in three ways: (1) a systems approach, which is used in clinical practice; (2) multitargeting features of the therapeutic method and preparations (the stage of the disease process is also considered); and (3) the ultra low-dose design of these preparations, which evokes multiple responses to a multitude of near-threshold stimuli produced by ultra low-diluted substances.

Multitargeted therapy becomes more and more the common buzzword in the medical and scientific community in light of increasing knowledge about the multifaceted nature of many diseases, especially chronic ones: increasing resistance to existing drugs, a decreasing number of new effective drugs, and a growing number of comorbidities in the aging population.<sup>2,3</sup> Targeting multiple pathways to reach optimal therapy has been favored when treating pneumonia,<sup>4</sup> dyslipidemia,<sup>5</sup> metabolic syndrome,<sup>6</sup> and many other diseases. Methodological approaches to multitargeted therapy in conventional medicine vary from combining

several drugs<sup>7,8</sup> or natural compounds,<sup>9</sup> which are expected to exert synergistic effects, to designing new drug entities by nanotechnologies<sup>10</sup> or genetic engineering.<sup>11</sup> However, although multitargeting can be seen as a relatively new trend in therapeutic approaches in modern conventional medicine,<sup>12</sup> traditional medical approaches, such as traditional Chinese medicine,<sup>13</sup> traditional phytotherapy,<sup>14</sup> and other holistic therapy concepts, have applied multitargeting in their practice since their creation.

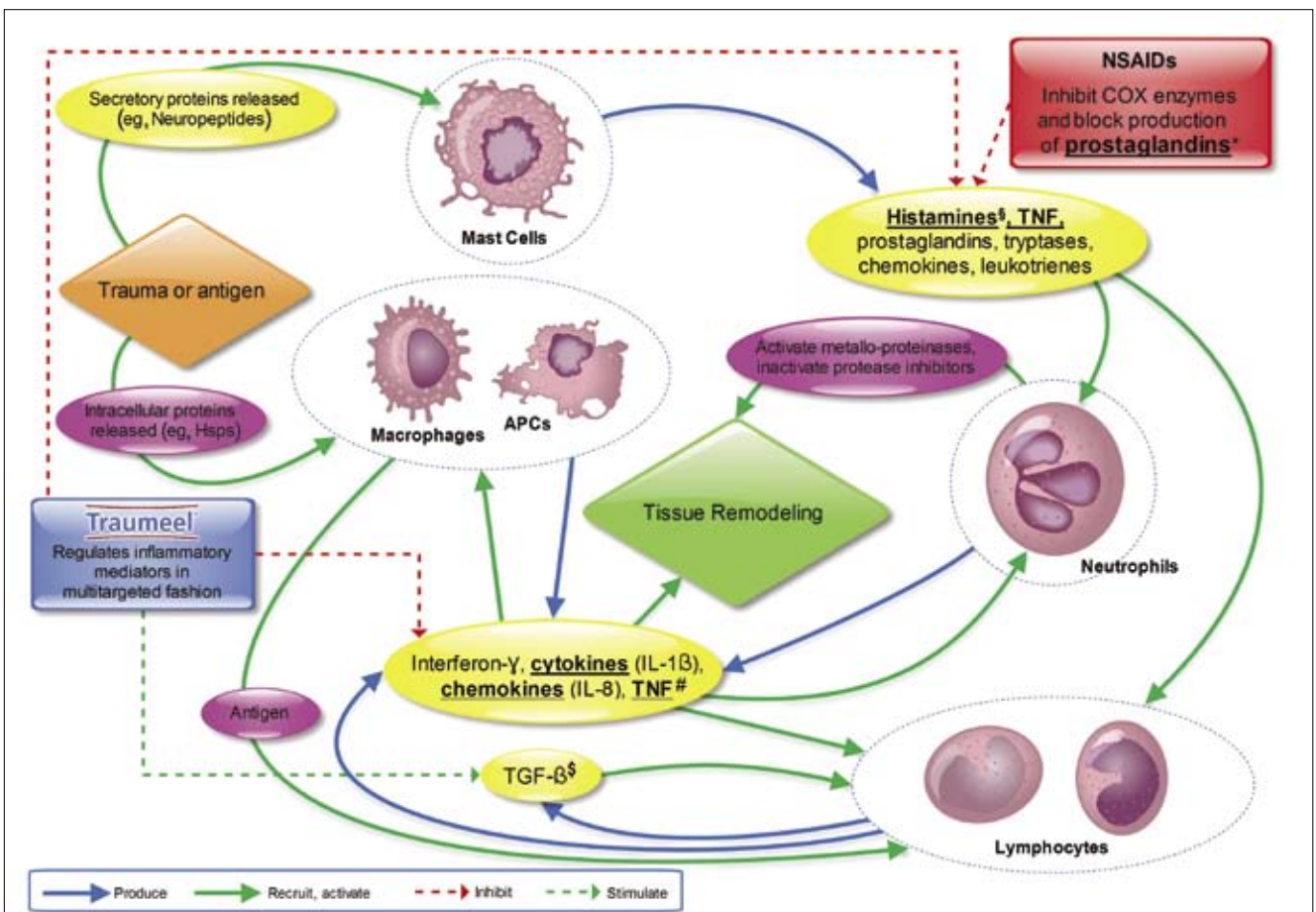
During the past few decades, knowledge about the ingenious complexity of human organisms, along with the complexity of common diseases and pathogenetic networks interrelating and connecting different organism systems, has been increasing. The image of a human being as an open and adaptive system that pursues the objectives of adaptation to the environment and survival has been repeatedly reinforced in the medical and scientific community.<sup>15,16</sup> Chapman et al,<sup>15</sup> in their perspective article, define “system” as a set of components constituting a whole within which a component interacts with or is related to at least one other component; ultimately, all components serve a common objective. Kaizu et al<sup>17</sup> emphasize that robustness against wide fluctuations (other than biological oscillations) in variables is considered a common design principle of a biological system. The view of such systems on the biology of the human organism has huge implications for medical thought because it encourages the medical community to sway more and more from a paradigm of treating major disorders and symptoms of the patient toward treating the patient as a whole unique system. Also, the system in this case possesses multiple options for responding to external interventions and displays a determination to sustain its own

activities.<sup>18</sup> The capability of the human organism to self-regulate to maintain homeostasis in a constantly changing external and internal environment via complex networks of feedback loops is a proposed target of many complementary medical systems, including traditional Chinese medicine,<sup>19</sup> acupuncture,<sup>20</sup> and bioregulatory medicine.<sup>1</sup>

One of such complex networks is an inflammatory network consisting of many inflammation-related components and their feedback loops, including cytokines, transcription factors, and regulatory genes.<sup>21-23</sup> This network plays a major role in the pathophysiological features of work-related musculoskeletal disorders (MSDs). For example, Xu and Murrell,<sup>24</sup> in their hypothesis of the pathogenesis of tendinopathy, suggest a model of interrelations between different functional networks, such as oxidative stress, apoptosis, matrix remodeling, tissue regeneration, and angiogenesis. It is well accepted that components of these functional networks are also regarded as players in inflamma-

tion-related processes. For example, reactive oxygen species may be essential secondary messengers signaling NLRP3/NALP3 (NOD-like receptor family, pyrin domain containing 3/NACHT, LRR, and PYD domains containing protein 3) inflammasome activation<sup>25</sup> or glucocorticoid receptors, which are implicated in programmed cell death, may change nuclear factor  $\kappa$ B-dependent transcription.<sup>26</sup> The role of the inflammatory network in the pathophysiological features of work-related MSDs is well described by Barbe and Barr.<sup>27</sup>

Current pharmacological treatment approaches of MSDs are directed toward suppression of proinflammatory players of the previously mentioned network and involve the use of conventional antiinflammatory agents, such as steroids or nonsteroidal antiinflammatory drugs.<sup>28</sup> On the other hand, bioregulatory medications, such as Traumeel, are aimed at the modulation of both proinflammatory and antiinflammatory pathways vs suppression (Figure 1).



**FIGURE 1** Role of Traumeel in the Inflammation Cascade (Adapted From Nathan<sup>23</sup>)

Each cell commits to recruiting and activating other cells based on multiple inputs, generally requiring evidence of both injury and infection (not shown) before it joins fully in amplifying the inflammatory process. Interactions among leukocytes, endothelium, platelets, and coagulation factors; the generation of stop signals; and the flow of information over subsequent days, including the transition to wound healing, are not shown. \*The inhibition of prostaglandins by nonsteroidal antiinflammatory drugs is not specified. <sup>8</sup>Data are taken from Baldwin and Bell. <sup>9</sup>Data are taken from Porozov et al. <sup>52</sup> <sup>9</sup>Data are taken from Heine and Schmolz. <sup>85</sup> APCs indicates antigen presenting cells; COX, cyclooxygenase; Hsps, heat-shock proteins; IL, interleukin; NSAIDs, nonsteroidal antiinflammatory drugs; TGF, transforming growth factor; TNF, tumor necrosis factor.

This is achieved by including into a formula several components of natural origin in microdoses and ultra low doses that purportedly act synergistically in a multitargeted manner on various players of the inflammation network. As previously shown, many substances of various origins have biological activities in dose ranges from  $10^{-2}$  to  $10^{-24}$  or even higher dilution. Examples include the neuroprotective effects of ultra low-dose glutamate,<sup>29,30</sup> the inhibition of opioid-induced hyperalgesia by ultra low-dose naltrexone,<sup>31</sup> the inhibition of proinflammatory cytokines and the reversal of the downregulation of L-glutamate transporters by ultra low-dose naloxone,<sup>32</sup> the antigenotoxic effects of homeopathic cadmium,<sup>33</sup> liver protection by ultra low-dose *Chelidonium majus*,<sup>34</sup> the inhibition of angiogenesis by paclitaxel at ultra low concentrations,<sup>35</sup> the improvement of memory by ultra low doses of antibodies to S-100B antigen,<sup>36</sup> and the cytotoxic effects to adenocarcinoma cells of ultra diluted *Carcinosin*, *Phytolacca*, *Conium*, and *Thuja*.<sup>37</sup> The clinical application of medications designed in ultra low doses is still debatable. In studies with peanut-allergic subjects, long-term desensitization was achieved by treatment with microdoses of peanut protein. Researchers hypothesized that allergen injection immunotherapy acts through downregulation of allergen-specific T-helper cell 2 responses, increased T-helper cell 1 responses, or the induction of T-regulatory cells; they found increased levels of T-regulatory cells and interleukin (IL) 10 in patient serum samples.<sup>38</sup> Manipulating immunological responses (eg, T-regulatory cells<sup>39</sup>) seems to be one of the possible ways to use microdoses or ultra low doses for therapeutic applications. Some researchers suggest that ultra diluted substances, through a so-called immunological bystander reaction, might be able to regulate the immune component of a disease.<sup>40</sup> Traumeel is usually used to treat disorders associated with acute inflammatory conditions of the musculoskeletal system (better known as MSDs), such as ankle sprains,<sup>41</sup> work-related tendinopathies,<sup>42</sup> muscle strains,<sup>43</sup> and short-term injuries.<sup>44</sup>

As the US National Research Council and the Institute of Medicine describe, MSDs involving the upper extremities, the lower extremities, and the back are an important national health problem.<sup>45</sup> In their publication, they state that MSDs are one of the leading categories of injuries and illnesses in the workplace, resulting in high levels of pain, discomfort, lost work time, and disability<sup>45</sup>; therefore, a need for further research was clearly defined. Several research groups suggested pathophysiological models of MSDs, either as a specific indication (eg, tendinopathy<sup>24</sup>) or in perspective of systems biology.<sup>27</sup>

This article discusses how the evidence from preclinical studies with Traumeel fits with current pathophysiological models of work-related MSDs. The aim is to provide a view on the assumptions of possible mechanisms of action of Traumeel as a multicomponent and multitargeted medication.

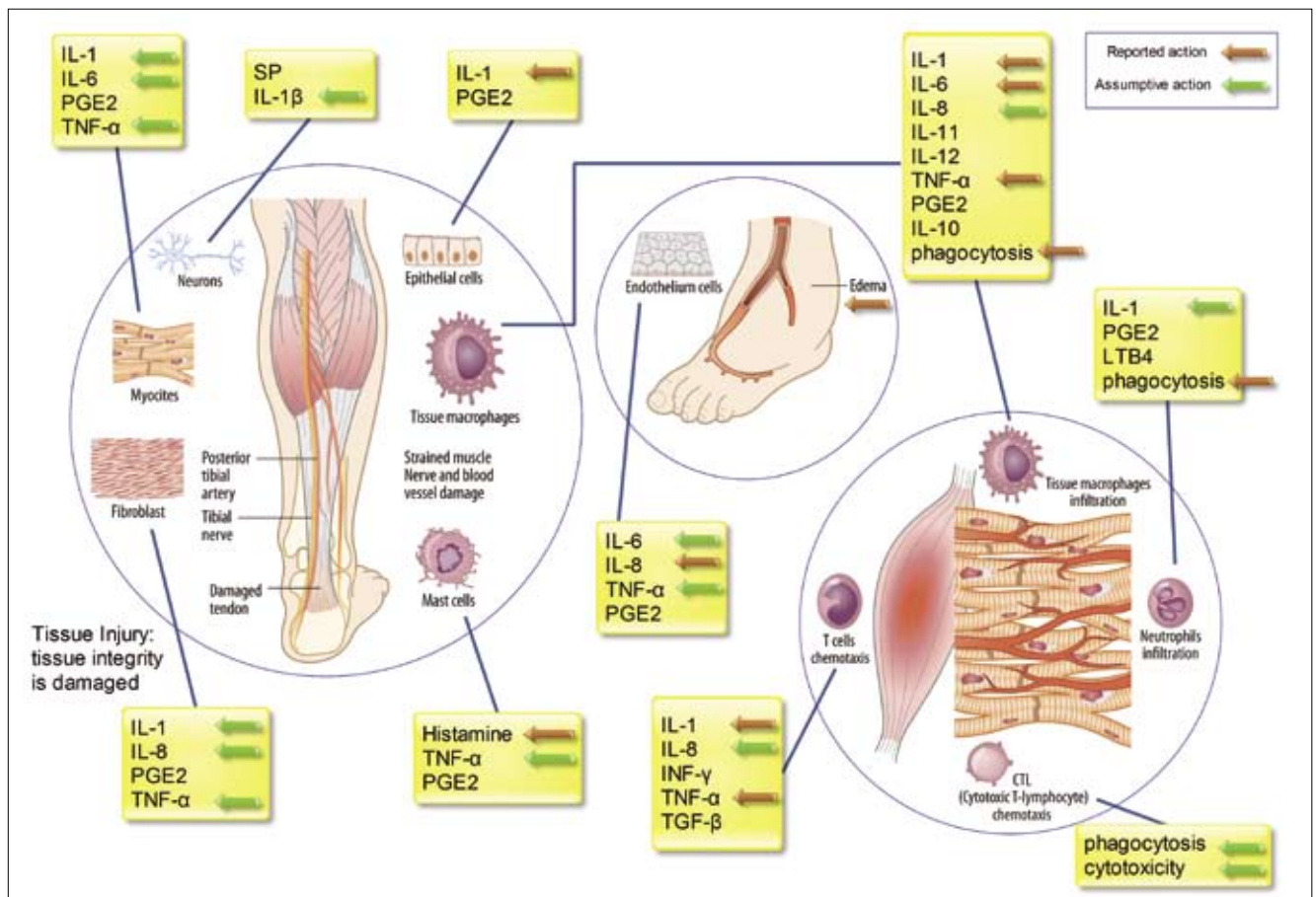
## REVIEW OF EVIDENCE FROM PRECLINICAL RESEARCH Model of Work-related Musculoskeletal Disorders and Proposed Contribution of Traumeel on Tissue Injury and Inflammation

To build a modeled overview of possible contributions of

Traumeel to the pathophysiological features of MSDs, the pathophysiological model of work-related MSDs, suggested by Mary F. Barbe, PhD, and Ann E. Barr, PhD,<sup>27</sup> was adopted in this publication. Their model is drawn based on extensive reviews of available evidence<sup>46,47</sup> and supported by their work with experimental rat models.<sup>48</sup> This model provides a comprehensive overview of work-related MSDs and can give insights into a potential therapeutic intervention with multitargeted therapies and/or medications.

The researchers suggest that inflammation plays a central role in MSDs related to overuse injuries. Also, physiological inflammation is required to repair damaged tissue.<sup>49</sup> Balanced cytokine release is postulated to be a key to tissue recovery<sup>50</sup>; therefore, acute inflammation (if not too robust) is beneficial, whereas chronic inflammation is detrimental.<sup>51</sup>

Per the model, primary tissue damage causes cellular release of cytokines (ie, mediators of inflammation, cell proliferation, cell migration, and regeneration). Peripheral tissue cell types (eg, fibroblasts, myocytes, and endothelial cells) respond to damage by upregulating several proinflammatory proteins; these proteins include IL-1, IL-6, tumor necrosis factor (TNF)  $\alpha$ , and prostaglandin  $E_2$ . Cytokines can also be released by other cell types (eg, dendritic and mast cells, neurons, and Schwann cells); those released during acute inflammation (eg, IL-1 $\alpha$ , IL-1 $\beta$ , and TNF- $\alpha$ ) mediate the proliferation and maturation of macrophages, other mononuclear cells, and fibroblasts. Then, activated macrophages and other mononuclear cells produce even more cytokines (eg, IL-1, IL-6, and IL-11), further stimulating inflammation (Barbe and Barr<sup>27</sup> reviewed this topic). Traumeel inhibits the secretion of proinflammatory cytokines (ie, IL-1 $\beta$ , IL-8, and TNF- $\alpha$ ) in resting and activated (mobile) immune cells and (resident) gut epithelial cells in vitro<sup>52</sup> (Figure 2). Local treatment with Traumeel was also associated with a significant decrease of systemic IL-6 levels.<sup>53</sup> Traumeel may target epithelial and/or endothelial cells, macrophages, and T cells and inhibit cytokine production. These effects might be responsible for fever reduction, the inhibition of such cellular behavior as T-cell and macrophage activation, T- and B-cell growth and differentiation, neutrophil migration, endothelium activation, and permeability.<sup>54</sup> IL-1 enhances the expression of cyclooxygenase-2, which is involved in the synthesis of prostanoids (eg, prostaglandin  $E_2$ ). IL-1 and TNF- $\alpha$  also serve as potent stimulators of osteoclast activity. According to Barr and Barbe, the "phagocytic action of the activated inflammatory cells and osteoclasts can result in direct tissue damage."<sup>46</sup> This leads to the initiation of chronic inflammation.<sup>46</sup> Although Traumeel is capable of stimulating phagocytosis and cell proliferation,<sup>55</sup> it also inhibits the IL-1 and TNF- $\alpha$  pathways. This multitargeted action prevents the vicious circle of reinforced tissue damage from activated inflammatory cells; rather, it modulates these cells toward tissue repair. The immunomodulating and beneficial phagocytosis-stimulating properties of Traumeel were supported by human research in patients with inflammatory periodontal disease and chronic generalized periodontitis.<sup>56,57</sup> In addition to epithelial cells and leukocytes, mast cells may be another important cellular target of



**FIGURE 2** Reported (orange) and Assumptive (light green) Targets for Traumeel's Action in Inflammation

Traumeel acts on multiple cellular targets during tissue injury and local acute inflammation. These targets include tissue and blood macrophages, T lymphocytes, neutrophils, mast cells, and epithelial cells. The "Model of Work-related Musculoskeletal Disorders and Proposed Contribution of Traumeel on Tissue Injury and Inflammation" subsection of the "Review of Evidence From Preclinical Research" section provides explanations. IL indicates interleukin; PGE, prostaglandin E; SP, substance P; TNF, tumor necrosis factor; LTB, leukotriene B.

Traumeel for modulation of inflammation. In the rat model of microvascular integrity, Traumeel significantly reduced noise-induced venular leakage of fluorescent albumin and degranulation of mast cells, suggesting reduced release of histamine.<sup>58</sup> Noise stress can lead to an excess of reactive oxygen species and inducible nitric oxide synthase (iNOS) in the walls of blood vessels of the cochlea stria vascularis.<sup>59</sup> The antiinflammatory properties of Traumeel were confirmed in animal models of acute inflammation (carrageenan-induced edema) and chronic inflammation (adjuvant arthritis). In these experiments, Traumeel led to a significant reduction of carrageenan-induced hind paw edema in the first model, and during the first week, a reduction of inflammation in the first phase of adjuvant arthritis treatment.<sup>60</sup>

Human research with Traumeel supports its antiinflammatory actions. In an open nonrandomized study of patients with mild rheumatoid arthritis, the influence of Traumeel (15 drops given three times per day for 14 days) on the number of CD4+ T lymphocytes, which are known to secrete transforming growth factor  $\beta$  (an important antiinflammatory cytokine), was studied and

evaluated.<sup>61</sup> A moderate increase in CD4+ T-lymphocyte numbers in most patients was observed. The researchers suggested that Traumeel might exert antiinflammatory effects via secretion of transforming growth factor  $\beta$  by these lymphocytes.<sup>61</sup>

#### Proposed Contribution of Traumeel to Tissue Reorganization

According to Barbe and Barr, the repetitive loading of bones, muscles, and tendons leads to adaptive remodeling of these tissues.<sup>27</sup> Early and discrete tissue injury stimulates an acute inflammatory response that may resolve with tissue repair in the presence of low repetition and low force; this may lead to advantageous adaptive remodeling. However, excessive repetitive loading may cause pathological remodeling/reorganization of tissues (eg, pathological remodeling of bone tissues into immature woven bone at sites of tendon and ligament attachments); myopathic changes, such as denervation and atrophy of muscle fibers, are stimulated, along with a fibrogenic response. This change can result in an increased susceptibility of the tissues to further reorganization and injury, with continued exposure leading

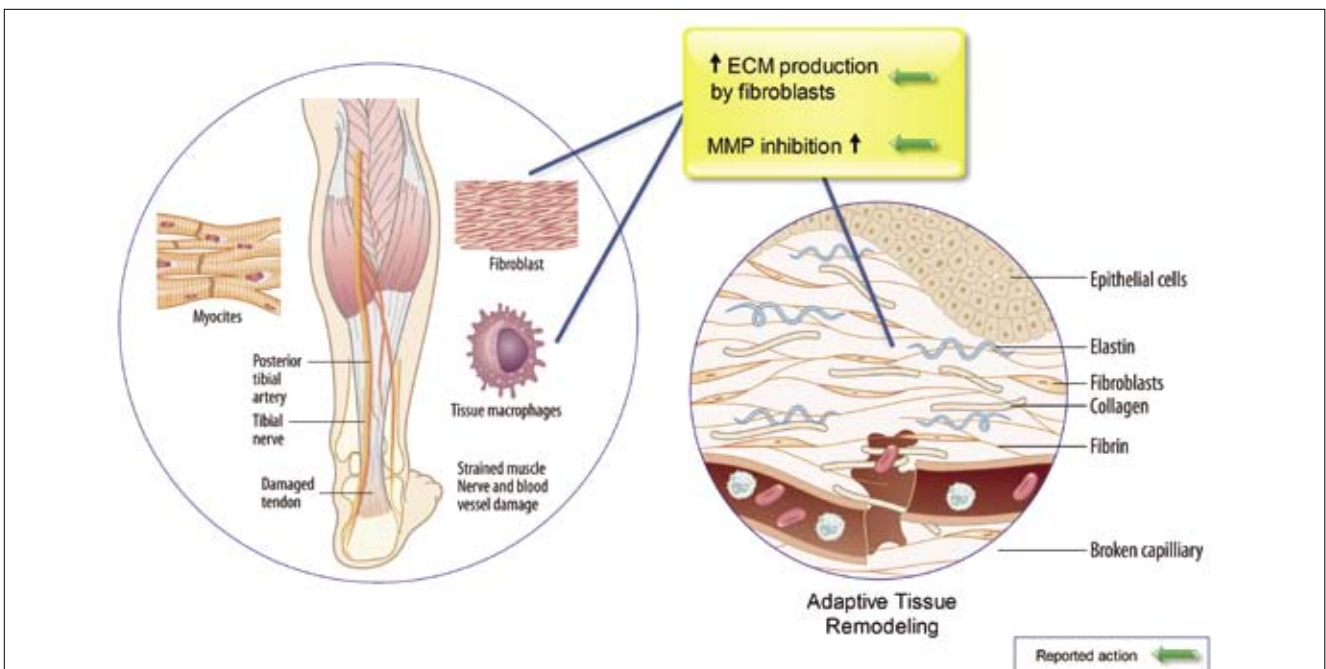
to reduced biomechanical tolerance and continued pathological remodeling. In some cases, there is no evidence of inflammation; in other studies, increased inflammatory cells and myopathic changes were found.<sup>27</sup> Some researchers argue that the interaction between exposure level, anatomical site, and nature of the task produces different tissue responses with respect to magnitude and/or timing.<sup>27</sup>

Some clues about Traumeel's possible contribution to tissue reorganization come from evidence reporting the properties of Traumeel ointment on the healing of experimentally induced wounds (Figure 3). One group of researchers investigated the influence of Traumeel on extracellular matrix (ECM) remodeling and wound healing properties in a coculture model with hepatocytes and hepatic stellate cells in vitro.<sup>62</sup> Traumeel reestablished the wound healing suppressed by the environmental toxin lindane. The researchers concluded that the protective effect of Traumeel may be because of reduced degradation or activated formation of ECM, attenuated migration and/or mobilization of granulocytes, or reduced susceptibility of hepatic stellate cells against lindane.<sup>62</sup> Another research group investigated dexamethasone-depressed wound healing in two rat wound models (namely, incision and dead space). In these experiments, Traumeel showed enhancement in breaking strength in incision wounds and time shortening during the epithelialization period. Moreover, the application of Traumeel locally to the wounds of animals systemically treated with dexamethasone significantly reversed the depressant effect of the steroid on all phases of

wound healing.<sup>63</sup> These findings indicate that ECM-producing cells (eg, hepatic stellate cells or fibroblasts) are likely targets for Traumeel's action in enhanced tissue repair and wound healing. Recently, it was reported that Traumeel increased the proliferation of cultured chondrocytes and stimulated glycosaminoglycan release. In addition, Traumeel significantly inhibited matrix metalloproteinase-13 expression, one of the matrix metalloproteinases used in ECM degradation.<sup>64</sup> These effects of Traumeel were independent of each other, suggesting multitargeted action of the preparation toward ECM restoration. Restoration of the proper extracellular environment is an important step in adaptive tissue remodeling; some researchers even suggest a xenogeneic approach for restoring ECM-based scaffolds to promote tissue reconstruction.<sup>65</sup> The important role of ECM-producing cells in tissue remodeling in muscle strain injury<sup>49</sup> and in liver injury<sup>66</sup> is well described. Evidence from the clinical application of Traumeel in the management of muscle strains supports its role in muscle tissue reorganization.<sup>43</sup>

### Characteristics of Individual Ingredients of the Traumeel Formula

Traumeel is a complex combination medication, composed of an orchestra of 13 ingredients of natural origin, including plant extracts and minerals. Although a detailed analysis of possible contributions of individual ingredients of Traumeel on a proposed model of work-related MSDs is out of the scope of this article, the literature was reviewed with the aim to identify the characteristic features of these ingredients, which could contribute to Traumeel's



**FIGURE 3** Reported Targets of Traumeel's Possible Action in Tissue Reorganization

Traumeel supports adaptive tissue remodeling after tissue injury. Traumeel modulates the function of extracellular matrix-producing cells (eg, fibroblasts and chondrocytes), supports granulation tissue formation, and inhibits some metalloproteinases to reduce tissue degradation. The "Proposed Contribution of Traumeel to Tissue Reorganization" subsection of the "Review of Evidence From Preclinical Research" section provides explanations. ECM indicates extracellular matrix.

**TABLE** Clinical Characteristics of Ingredients of Traumeel Based on a Literature Review

Properties	<i>Bellis</i>					<i>Hepar</i>		<i>Mercurius</i>		<i>Millefolium</i>	<i>Symphytum</i>		
	<i>Aconitum</i>	<i>Arnica</i>	<i>Belladonna</i>	<i>perennis</i>	<i>Calendula</i>	<i>Chamomilla</i>	<i>Echinacea</i>	<i>Hamamelis sulfuris</i>	<i>Hypericum</i>			<i>solubilis</i>	
<b>Effects</b>													
Immuno-modulatory	X <sup>67</sup>	X <sup>67</sup>		X <sup>67</sup>	X <sup>67</sup>	X <sup>67,86</sup>	X <sup>67,87-89</sup>	X <sup>67</sup>	X <sup>67,90</sup>	X <sup>67</sup>		X <sup>67</sup>	
Anti-inflammatory		X <sup>68-70</sup>	X <sup>71</sup>		X <sup>91</sup>	X <sup>92,93</sup>	X <sup>71,94</sup>	X <sup>95</sup>		X <sup>96,97</sup>		X <sup>98</sup>	X <sup>99</sup>
Antioxidative					X <sup>72</sup>	X <sup>100</sup>	X <sup>101</sup>	X <sup>102-104</sup>		X <sup>105</sup>		X <sup>98</sup>	
Antinociceptive										X <sup>96,106</sup>			
Antibacterial		X <sup>107,108</sup>		X <sup>109</sup>			X <sup>110</sup>	X <sup>95</sup>		X <sup>111,112</sup>		X <sup>98</sup>	
Antiviral					X <sup>73</sup>			X <sup>113</sup>		X <sup>112</sup>			
Wound-healing					X <sup>74,75</sup>					X <sup>74,114</sup>			X <sup>115</sup>
Mucosa protective												X <sup>116</sup>	
Anti-proliferative						X <sup>117,118</sup>				X <sup>112,119</sup>		X <sup>120</sup>	
Tissue reorganization							X <sup>76,77</sup>						
Anti-hemorrhagic								X <sup>121</sup>					
Spasmolytic					X <sup>122</sup>					X <sup>123</sup>		X <sup>124</sup>	

biological activities. For example, ultra low–diluted *Aconitum napellus* could influence the liberation of transforming growth factor  $\beta$  from leukocytes of healthy donors in whole blood cultures, as do *Arnica montana*, *Calendula officinalis*, *Chammomilla recutita*, *Echinacea*, sulphuric calcium, *Hypericum perforatum*, and *Symphytum officinale*.<sup>67</sup> Moreover, extracts of Arnica flowers show the capability of impairing the activation of the transcription factor nuclear factor  $\kappa$ B and the nuclear factor of activated T cells, the proteins that are responsible for the transcription of genes encoding various inflammatory mediators.<sup>68,69</sup> In ultra low doses, pretreatment with *A montana* blocked the action of histamine in increasing vascular permeability.<sup>70</sup> Extracts of *Atropa belladonna* and *Echinacea angustifolia* in ultra low doses modulate the peritoneal inflammation reaction and have a cytoprotective action on leukocytes.<sup>71</sup> Evidence suggests that *C officinalis* exerts free radical scavenging and antioxidant activity.<sup>72</sup> In addition, *C officinalis* may possess some antiviral capabilities.<sup>73</sup> Tinctures of *C officinalis* and *H perforatum* may facilitate the collagen maturation phase of wound healing<sup>74</sup>; on the other hand, an extract from *C officinalis* indicated potent wound-healing activity.<sup>75</sup> Other evidence indicates the antiinflammatory and wound-healing properties of *Echinacea pallida* and its constituent echinacosides.<sup>76</sup> These findings have been confirmed in a pig animal model.<sup>77</sup> The Table provides an overview of the possible clinical characteristics of the ingredients of Traumeel.

These few examples shed some light on the understanding of how different ingredients with multiple biological properties

could actually synergize their activities when combined in a complex formula and in a multitargeted fashion to achieve a clinically relevant outcome for a given indication (eg, MSDs).

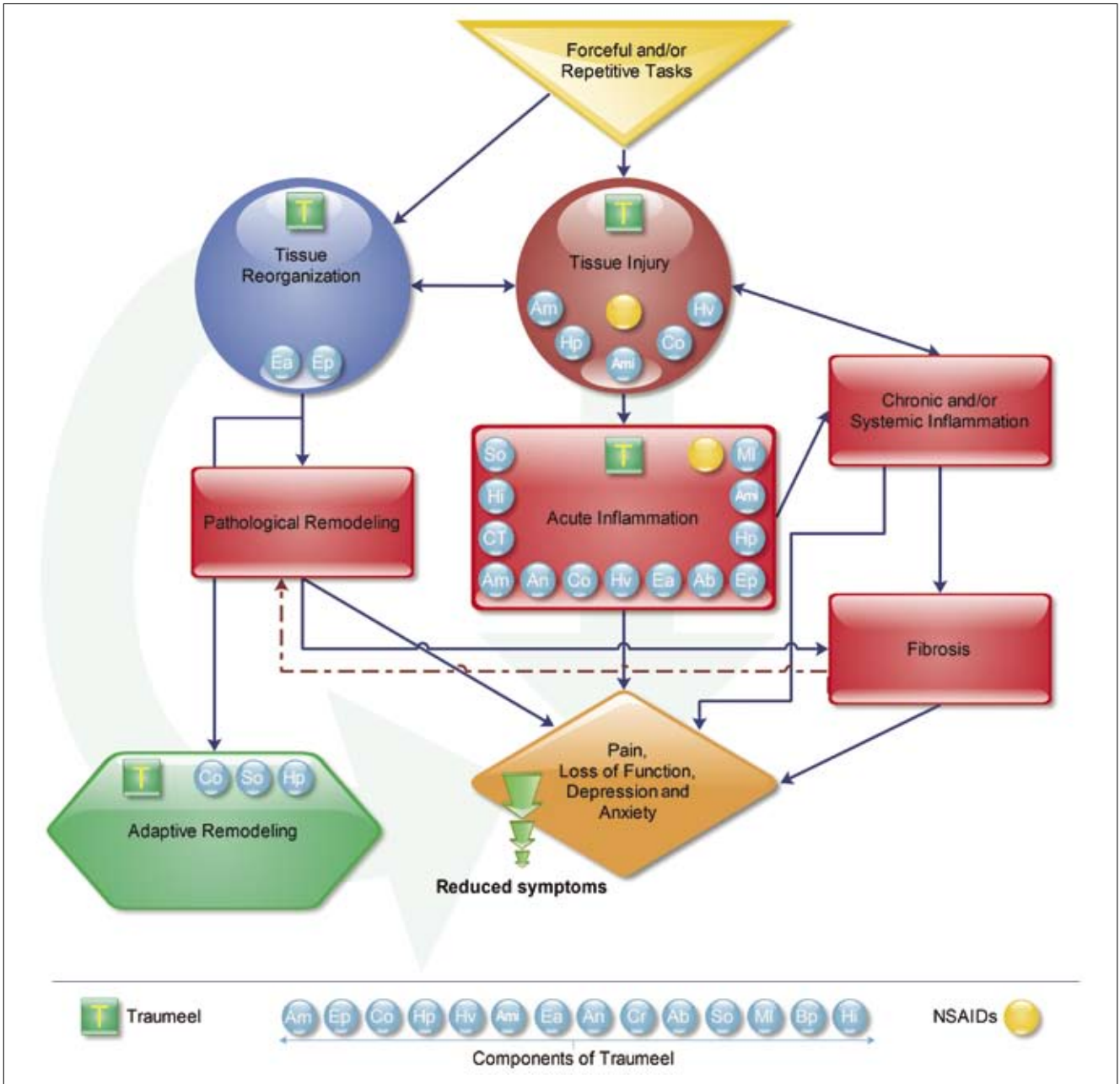
## DISCUSSION

Bioregulatory medicine is a systems-based approach that uses complex medications consisting of activated ultra diluted substances that act in a multitargeted fashion. It allows physicians to adjust the therapeutic regimen to the current condition of the patient. Therefore, the treatment can be adapted to meet the specific needs of the unique stage of an individual's disease. In the present article, the evidence from preclinical studies with the bioregulatory medication Traumeel was used to corroborate the current pathophysiological models of work-related MSDs. The aim was to provide a working hypothesis of the possible mechanisms of action of Traumeel (a multicomponent and multitargeted complex preparation) within such a model. Another aim was to discuss what place bioregulatory therapy can have in the understanding of modern disease evolution and what treatment options this therapy can suggest.

Current scientific knowledge suggests that Traumeel can be a useful addition to the management of work-related MSDs. For example, Traumeel modulates inflammatory pathways by down-regulating proinflammatory cytokines and upregulating antiinflammatory cytokines, reducing edema,<sup>60,78</sup> promoting phagocytosis,<sup>55-57</sup> and improving wound healing.<sup>58,62</sup> Adaptive tissue remodeling is supported by Traumeel acting on the behavior

of ECM-producing cells and inhibiting metalloproteinases.<sup>64</sup> This evidence supports and is in line with the pathophysiological model of work-related MSDs; the model suggests that tissue injury, acute inflammation, and tissue reorganization are among the major pathways implicated in the pathophysiological features of these diseases (Figure 4).

It is typical for all biological therapies that their modes of action still need to be fully elucidated. The weakness of the hypothesis of Traumeel's modes of action, suggested in this article, is that many of the proposed biological effects of the individual ingredients of Traumeel have been extrapolated from well-designed studies in botanical medicine that used different



**FIGURE 4** Overview of Possible Sites of Action of Traumeel and Its Ingredients in the Pathophysiological Model of Repetitive Overuse Task-related Musculoskeletal Disorders

Traumeel plays a role in multiple pathophysiological processes (inflammation and tissue reorganization). The modulation of these processes toward successful resolution is the key feature of multitargeted action. In contrast, nonsteroidal antiinflammatory drugs act only in distinguished pathophysiological processes (ie, the arachidonic pathway in acute inflammation) by suppressing them. The ingredients of the Traumeel formula are as follows: Ab, *Atropa belladonna*; Am, *Arnica montana*; Ami, *Achillea millefolium*; An, *Aconitum napellus*; Bp, *Bellis perennis*; Co, *Calendula officinalis*; Cr, *Chamomilla recutita*; Ea, *Echinacea angustifolia*; Ep, *Echinacea purpurea*; Hp, *Hypericum perforatum*; Hs, *Hepar sulfuris* (calcium sulfide); Hv, *Hamamelis virginiana*; Ms, *Mercurius solubilis* (mercurio-amidonitrate); So, *Symphitum officinale*. T in the box indicates Traumeel.



doses and preparation forms. Nevertheless, it is possible that the biological targets of these effects might be similar irrespective of the dose. For example, in the case of hormetic-type responses, therapeutic effects swing around the same targets (eg, cell viability/toxicity) but with a different modality (stimulatory/inhibitory) in a nonlinear dose-response manner.<sup>79</sup> In other cases, the effects respond linearly. Crippa et al reported that the combination of endothelial monocyte-activating polypeptide II and TNF- $\alpha$ , both in ultra low doses, synergistically acted on the same target (neovascularization) as in higher doses but showed reduced toxicity.<sup>80</sup> In both cases, the extrapolation of the action of a substance in an ultra low dose is possible given that the target of this action is known. Therefore, the evidence from studies with concentrated plant extracts could provide hints about which molecular networks (not necessarily the same molecular targets) might be the goals of the ultra diluted substances. Evidence from preclinical Traumeel studies supports this notion, showing that the targets of its actions (eg, immunocompetent cells) are also targets of many of its ingredients in plant extract-high concentrations.

There are additional aspects unique to a bioregulatory preparation such as Traumeel regarding its biological targeting features. These aspects include the following: (1) multitargeting, which can be described as a nonlinear summation of biological activities of the ingredients; (2) the fact that multitargeting is necessary to reset the compromised autoregulatory network pattern, in which a multitude of near-threshold stimuli generate several responses and increase autoregulating system robustness; and (3) effectiveness in resolving the pathophysiological pattern, which lies in the synergy of these stimuli and responses. This synergy is not a linear sum of effects of ingredients; rather, it is a specific pattern of biological activities, defined by the combination design of a bioregulatory preparation. Thus, excluding one ingredient from the formula could potentially change the synergistic pattern and alter the properties of a preparation. These features distinguish Traumeel-type preparations from other biological response modifiers, such as infliximab (Remicade), a monoclonal antibody against TNF- $\alpha$ , which has a distinctive mechanism of action of linearly inhibiting one of the master regulators of inflammation-related mechanisms.<sup>81</sup>

The totality of preclinical research suggests that Traumeel has a remarkable scope of action on the pathophysiological processes of work-related MSDs. The strength of the evidence is its role as an immunomodulator. However, there are several potential gaps in its mechanisms of action. For example, despite its broad multitargeted action, Traumeel does not cover all of the pathophysiological pathways of work-related MSDs, as shown in Figure 4. The role of Traumeel as an intervention for central nervous system reorganization still needs to be defined. The coverage of the whole spectrum of pathophysiological events can be achieved by supplementing the treatment with other medications (ie, mainstream and/or bioregulatory preparations) targeted to the modulation of nervous functions. This approach would allow the formulation of treatment concepts with almost com-

plete coverage of all possible pathophysiological networks around any given disorder and would ensure effective and robust resolution of a clinical pathological feature.

Further preclinical studies should be performed with Traumeel to expand the present knowledge of its potential mechanisms of action and to confirm the existing data. The evidence presented herein is still preliminary, and the bioregulation concept itself is in the early stages of development. Nevertheless, the need for discussions exploring scientific assumptions and revealing the gaps in knowledge is widely recognized in the complementary and alternative medicine and traditional medicine communities.<sup>82,83</sup> Further investigations are certainly required to fill these gaps in evidence, using even cutting-edge technologies.

This article presented a specific view on evidence from preclinical research performed with Traumeel, with the aim of providing a plausible hypothesis of mechanisms of action of a complex ultra low-dose medication with bioregulatory properties. Also, the article tries to reflect how the concepts of bioregulation and multitargeting fit to evolving the present understanding of disease complexity and the need to properly address this complexity in a clinical world.

## CONCLUSIONS

Increasing scientific knowledge regarding the complexity of biological and physiological processes, boosted by modern technological advances (“-omics” technologies), forces the reevaluation of the current concepts of disease development and moves information from a linear and reductionist view to a complex and network-shaped systems’ perception of pathophysiological events defining disease pathogenesis and evolution.<sup>84</sup> The application of systems-based biology concepts in the biomedical field calls for novel therapeutic concepts and approaches that would integrate the systems perspective in the management of complex diseases. Multitargeting is one of these concepts; it allows the application of therapeutic effort to the disease pathophysiological pattern rather than to a single pathophysiological event. Multiple approaches to multitargeting are suggested; the application of bioregulatory therapeutics, which are characterized as combinations of multiple ultra low-diluted substances, is one of them. The current evidence suggests that Traumeel displays nonlinear biological activities in addition to synergistic modes of action and supports its value in treating multifaceted disorders (work-related MSDs) from the systems perspective. Bioregulation is a cutting-edge concept that is increasingly accepted by and integrated into mainstream medical care. Future research will increase the scientific knowledge necessary to support the principal concepts of bioregulatory medicine.

## Disclosure

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# Review of the Clinical Efficacy of the Multicomponent Combination Medication Traumeel and Its Components

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**Objective** • Musculoskeletal injuries and inflammation are the most common indications for use of the multicomponent combination medication, Traumeel. This article reviews the clinical evidence for the safety and efficacy of Traumeel and discusses its use as an alternative to nonsteroidal antiinflammatory drugs (NSAIDs).

**Methods** • A systematic database search for pharmacological and clinical studies and case reports of Traumeel and its constituents in registered and unregistered indications was conducted. The immunomodulatory mode of action, safety, and efficacy of Traumeel was reviewed.

**Results** • Six randomized, controlled studies; 19 nonrandomized, controlled studies; four cohort studies; and numerous case reports investigating the different application forms of Traumeel (injection solution, tablets, drops, ointment, gel) were identified. Various preclinical and clinical investigations with the constituents were also found. Unlike conventional NSAIDs, Traumeel does not directly inhibit prostaglandin synthesis. It has antioxidative and immunomodulatory properties and appears to modulate arachidonic acid by decreasing the

activity of phospholipase A2. Traumeel is reported to provide effective pain relief and reduce inflammation in patients with acute and subacute musculoskeletal disorders, physical trauma, and sport injuries. Successful treatment of hemarthrosis-related effusions and a reduction of joint pain associated with fibromyalgia was also demonstrated. Traumeel ointment reduced swelling and improved joint mobility in patients with sport-related ankle sprain. There is also evidence that Traumeel is of comparable efficacy to NSAIDs in the treatment of epicondylitis and tendinosis. Data from clinical studies and reports during more than 60 years of use in clinical practice support the excellent safety profile of Traumeel. The risk of hypersensitivity or allergic reactions is very low.

**Conclusions** • Rapid pain relief and antiinflammatory effects were observed in patients with acute or subacute musculoskeletal problems treated with Traumeel. Traumeel may be considered an effective and well-tolerated alternative to NSAIDs for the first-line treatment of physical trauma and sport injuries. (*Altern Ther Health Med.* 2011;17(2 Suppl):S18-S31.)

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**T**he multicomponent combination medication, Traumeel (Biologische Heilmittel Heel GmbH, Germany) is widely used for physical trauma, sport injuries, and degenerative and immunological disorders. It contains 12 botanical and two mineral substances in micro- or ultra low-dilutions. Traumeel has pronounced analgesic, antiedematous, and antiexudative effects, and treatment results in rapid reduction of inflammation, pain relief, recovery from bruising, and healing promotion.

The clinical use of Traumeel is based on the bioregulatory understanding of the origin of diseases and their cures. The bioregulatory concept defines illnesses as defense mechanisms against harmful exogenous and endogenous substances. Such harmful substances, originally called homotoxins by Hans Heinrich

Reckeweg, impair the balance between the extracellular matrix (ECM) and cellular metabolism. In bioregulatory medicine, achieving a bioregulatory balance between pro- and antiinflammatory cytokines is considered to be the critical step in recovery.

Reckeweg's bioregulatory concept has many aspects in common with the modern understanding of immunology, such as psycho-neuro-endocrine-immunological complexity. It includes modern hypotheses for the mode of action of micro- or ultra low-dose solutions such as the immunological bystander reaction,<sup>1</sup> and integrates the reticuloendothelial and the adeno-hypophyseal systems, neural reflexes, connective tissue detoxification functions, and liver detoxification.<sup>2</sup>

The dynamic view of disease states and defense mechanisms against harmful substances allows prediction of possible further developments of the pathological condition (progression or regression). Reckeweg defined six phases of action, with phases 1, 2, and 3 being humoral (the excretion, inflammation, and deposition phases, respectively) and phases 4, 5, and 6 being cellular (the impregnation, degeneration, and neoplasm phases, respectively). Changes in pathological condition are called vicariation, which includes improvement (regressive vicariation) and

worsening (progressive vicariation). The objective of bioregulatory treatment, such as with Traumeel, is regressive vicariation.

Alfred Pischinger developed a theory based on the regulation of the ECM (“ground regulation”). He defined this system as a functional unit comprising the final vascular pathway, the connective tissue cells, and the final vegetative-nervous structure containing cellular elements like fibrocytes and immune cells. Among these cells and structures, the extracellular fluid and associated lymph system create the “milieu interior” (or ECM), which is the area of basic vital functions and body self-regulation. Pischinger postulated that all organs and cellular components are dependent on the dynamic flow in the ECM, which responds to stimuli and is the origin of many immunological and pathological actions (eg, inflammation).<sup>3</sup>

According to Reckeweg, acute inflammation is an action by the ECM to remove disease-producing harmful substances. In his theory, chronic inflammation can be understood as “disease provoking” due to suppression of inflammation, recurrent infection, intoxication, or autoimmunity. Medications with bioregulatory properties, such as Traumeel, might engage the inflammatory response to repair physiological damage within the patient without affecting the self-regulating control of the inflammatory process. These medications are not only symptom-specific, but also patient-specific. As addressed in the article by Cesnulevicius in this supplement, which discusses possible biological activities of Traumeel within the pathophysiological model of overuse musculoskeletal disorders, these medications don’t simply suppress the symptoms, but support metabolism and immune responses in the framework of a given autoregulatory system.

This article reviews the evidence supporting the clinical use of Traumeel. Particular focus is on the contribution of immunomodulatory and antiinflammatory effects to Traumeel’s broad clinical efficacy. Additionally, the clinical use of Traumeel as an equally effective but better tolerated alternative to nonsteroidal antiinflammatory drugs (NSAIDs) is presented. A bioregulatory treatment approach might be considered particularly beneficial to patients with poor tolerance to NSAIDs. Unlike conventional NSAIDs, Traumeel does not inhibit the arachidonic pathway of prostaglandin and comparisons are made between the different modes of action.

## METHODS

### Formulations

Five different galenic application forms of Traumeel are currently marketed, including injection solution, tablets, drops, ointment, and gel. The composition of each formulation is presented in Tables 1 through 3.

### Registered Indications

**Systemic Application Forms.** The systemic application forms of Traumeel are injection solution, tablets, and drops. Registered indications for these forms of administration include blunt injuries (eg, sprains, dislocations, contusions, hemarthrosis, and effusions into a joint); fractures; postoperative and posttraumatic edema and swelling of the soft tissues; inflammatory and

**TABLE 1** Composition of Traumeel Injection Solution

Component	Dilution	Injection Solution* (2.2 mL)
<i>Arnica montana</i>	D2	2.2 µL
<i>Calendula officinalis</i>	D2	2.2 µL
<i>Hamamelis virginiana</i>	D1	0.22 µL
<i>Achillea millefolium</i>	D3	2.2 µL
<i>Atropa belladonna</i>	D2	2.2 µL
<i>Aconitum napellus</i>	D2	1.32 µL
<i>Mercurius solubilis Hahnemanni</i>	D6	1.1 µL
<i>Hepar sulfuris</i>	D6	2.2 µL
<i>Chamomilla recutita</i>	D3	2.2 µL
<i>Symphytum officinale</i>	D6	2.2 µL
<i>Bellis perennis</i>	D2	1.1 µL
<i>Echinacea angustifolia</i>	D2	0.55 µL
<i>Echinacea purpurea</i>	D2	0.55 µL
<i>Hypericum perforatum</i>	D2	0.66 µL

\*Contains water for injection and sodium chloride.

**TABLE 2** Composition of Oral Preparations of Traumeel

	Dilution	1 tablet*	Drops† (100 g)
<i>Arnica montana</i>	D2	15 mg	5 g
<i>Calendula officinalis</i>	D2	15 mg	5 g
<i>Hamamelis virginiana</i>	D2	15 mg	5 g
<i>Achillea millefolium</i>	D3	15 mg	5 g
<i>Atropa belladonna</i>	D4	75 mg	25 g
<i>Aconitum napellus</i>	D3	30 mg	10 g
<i>Mercurius solubilis Hahnemanni</i>	D8	30 mg	10 g
<i>Hepar sulfuris</i>	D8	30 mg	10 g
<i>Chamomilla recutita</i>	D3	24 mg	8 g
<i>Symphytum officinale</i>	D8	24 mg	8 g
<i>Bellis perennis</i>	D2	6 mg	2 g
<i>Echinacea angustifolia</i>	D2	6 mg	2 g
<i>Echinacea purpurea</i>	D2	6 mg	2 g
<i>Hypericum perforatum</i>	D2	3 mg	1 g

\*Contains lactulose monohydrate; †Contains 35 vol-% alcohol.

degenerative processes associated with inflammation, arthrosis of the hip, knee, and small joints; and acute cerebral contusions.

**Topical Application Forms.** Topical application forms include an ointment and gel. Traumeel ointment and gel are indicated for blunt injuries (eg, sprains, dislocations, contusions, hemarthrosis, and effusions into a joint), closed fractures, inflammatory and

**TABLE 3** Composition of Topical Traumeel Preparations

	Dilution	Ointment* (100 g)	Gel† (100 g)
<i>Arnica montana</i>	D3	1.5 g	1.5 g
<i>Calendula officinalis</i>	Æ	0.45 g	0.15 g
<i>Hamamelis virginiana</i>	Æ	0.45 g	0.15 g
<i>Echinacea angustifolia</i>	Æ	0.15 g	0.15 g
<i>Echinacea purpurea</i>	Æ	0.15 g	0.15 g
<i>Chamomilla recutita</i>	Æ	0.15 g	0.15 g
<i>Symphytum officinale</i>	D4	0.1 g	0.1 g
<i>Bellis perennis</i>	Æ	0.1 g	0.1 g
<i>Hypericum perforatum</i>	D6	0.09 g	0.09 g
<i>Achillea millefolium</i>	Æ	0.09 g	0.09 g
<i>Aconitum napellus</i>	D1	0.05 g	0.05 g
<i>Atropa belladonna</i>	D1	0.05 g	0.05 g
<i>Mercurius solubilis Hahnemanni</i>	D6	0.04 g	0.04 g
<i>Hepar sulfuris</i>	D6	0.025 g	0.025 g

\*Based on hydrophilic ointment (DAB), preserved with 12.5 volume-% alcohol;  
†contains 25% alcohol; D, dilution; Æ, *Tinctura Mater* (Mother Tincture).

degenerative processes (particularly of the tissues providing support and mobility), and arthrosis of the hip, knee, and small joints.

### Search Strategy

A comprehensive literature search of AMED, Medline, Embase, and the Cochrane library to identify all studies on Traumeel and its constituents was performed. All common and scientific names of Traumeel and its constituents were used to identify the studies. All Traumeel literature published between 1966 and March 2007 reporting efficacy in humans, dosing, precautions, adverse events (clinical and laboratory parameters), use in pregnancy/lactation, and mode of action were included in the review. The search for published articles investigating the constituents of Traumeel focused on the period from January 2000 to March 2007, although the reference lists of earlier studies were also scanned for important studies for inclusion.

### Evaluation

All clinical studies on Traumeel and/or its constituents were reviewed, listed, and reported. Studies investigating Traumeel and those reporting on its constituents were reviewed separately. The quality of the randomized, controlled trials was assessed using the Jadad score,<sup>4</sup> a validated instrument for measuring the methodological quality on a scale of 0 (poor) to 5 (good).

### Analysis

Clinical efficacy and safety data on Traumeel, its constituents, and placebo and active controls were reviewed in the context of findings from modern immunological research. Several

mechanisms probably contributing to the clinical efficacy of Traumeel in several indications were discussed, along with the possible effects of the constituents on immunological processes.

## RESULTS

### Overview of Studies and Investigations

**Preclinical Investigations.** In preclinical investigations, Traumeel showed a broad range of antiinflammatory and immunomodulatory effects in vitro and in vivo. Wound healing and antioxidative effects were also demonstrated in animal models.

**Clinical Efficacy.** The Traumeel clinical trial program included six randomized, controlled studies; 19 nonrandomized, controlled studies; and four cohort studies (Table 4). There are also numerous case reports detailing the use of Traumeel. All five galenic forms of Traumeel (injection solution, tablets, drops, ointment, and gel) were studied in a broad range of registered and unregistered indications.

### Efficacy in Registered Indications

**Acute Sport Injuries.** In a randomized, double-blind study investigating treatment effects on joint mobility (primary efficacy variable), pain on motion, and angulations of supination (affected joint vs nonaffected contralateral joint), Traumeel ointment (n = 36) was compared to placebo (ointment base; n = 37) in patients with ankle sprains.<sup>5</sup> All patients also received electrotherapy as a basic treatment. Traumeel ointment significantly improved joint mobility at day 10 ( $P < .05$ ) and pain on motion ( $P < .0001$ ). The study was considered to be well conducted and reported (Jadad score = 4), although the randomization procedure was not described.

In another randomized, double-blind study, 102 patients with acute sport injuries (sprains, contusions grade 1-2) were treated with Traumeel S ointment (n = 34), Traumeel-Sine (contains five compounds only; n = 34), or placebo (ointment base; n = 34).<sup>6</sup> Treatment (2 x 10 g ointment daily) was started at latest on day 4 after the injury. Swelling (primary objective) was substantially reduced by Traumeel at day 15, but the reduction vs placebo was statistically significant for the Traumeel Sine group only. Increase in maximum muscle force, reduction of pain, and time to resumption of training were superior for patients in the Traumeel group. The methodological quality of this study was good (Jadad score = 4) and included descriptions of randomization, statistical evaluation, inclusion/exclusion criteria, and continuous quality assurance during the trial.

In a comparison between Traumeel S ointment (n = 25) and Traumeel S ointment plus galvanic electricity (n = 25) in competitive athletes with lateral ligament overextension of the malleolar (supination-distorsion trauma), pain at rest was reduced in both treatment groups up to day 7.<sup>7</sup> However, Traumeel monotherapy had a more pronounced affect on pain from pressure and pain on motion.

Traumeel S drops (3 x 10 drops/day) were compared with conventional standard therapy in 75 patients with soft tissue contusions and fractures in a nonrandomized study. Treatment success was observed in most patients within 5 days.<sup>8</sup> There was

evidence of a dose-related effect; 3 x 30 drops/day appeared to be more effective than 3 x 10 drops/day. A dose-related effect was also observed in a comparison between Traumeel S drops 3 x 15 drops/day and 3 x 10 drops/day as add-on treatment to Traumeel ointment.<sup>9</sup> After removal of the plaster cast, the higher dose seemed to reduce the circumference of the affected extremity more effectively than the lower dose in 26 patients with soft tissue swelling due to bone fractures.

Further evidence of the efficacy of Traumeel ointment was observed in a multicenter drug monitoring trial, which included 3422 patients with different musculoskeletal injuries.<sup>10</sup> The efficacy of Traumeel was assessed as “very good” or “good” in 48.3% and 38.4% of patients, respectively.

**Hemarthrosis.** A randomized, double-blind study comparing Traumeel injection solution (2 mL intra-articular injections on days 1, 4, and 8) with placebo (2 mL intra-articular injections of sodium chloride solution on days 1, 4, and 8) in 73 patients with injury-related hemarthrosis of the knee demonstrated that Traumeel was superior to placebo in assessments of joint circumference and mobility, pain intensity, and effusion volume.<sup>11</sup> However, the methodological and reporting of this study was poor (Jadad score=1).

In patients with acute traumatic effusions of the knee joint (hemarthrosis and hydrarthrosis), Traumeel injection (2.2 mL intra-articular injection) after hematoma aspiration reduced the rate of recurrence after 3 weeks compared to standard basic treatment.<sup>12</sup> A total of 89% (25/28) of patients treated with Traumeel were without detectable effusions compared with 21% (4/19) patients in the control group.

**Epicondylitis.** In an open-label, nonrandomized, multicenter study, treatment with local injections (2.2 mL) of Traumeel S were compared with intramuscular injections of NSAIDs (mainly diclofenac) in 184 patients with epicondylitis.<sup>13</sup> Additional treatments and physiotherapy were permitted during the observation period of 2 weeks, but patients receiving Traumeel could not receive NSAIDs and patients receiving an NSAID could not receive micro- or ultra low-diluted remedies. The study provided evidence for the noninferiority of Traumeel with regard to NSAIDs. Significantly greater improvement in pain at rest and mobility (change in torsional and extensional joint mobility) was reported following treatment with Traumeel compared with NSAIDs.

**Tendinosis.** Patients with tendinosis were studied in an open-label, nonrandomized, controlled study comparing thermotherapy (Hydrosun; n = 84), Traumeel injections (2 x 1 ampoule [2 mL] injection solution per week; n = 48), and the combination of thermotherapy plus Traumeel injections (2 x 1 ampoule [2 mL] injection solution per week; n = 79).<sup>14</sup> Traumeel was mixed with mecaïne 1% and injected into the tender points; treatment was administered for 4 to 6 weeks. Traumeel injections alone were found to be the most effective treatment, followed by combination therapy. Pre- and posttreatment assessments using a visual analogue scale (VAS) showed that pain levels in patients receiving Traumeel monotherapy improved significantly after 3

to 4 weeks ( $P < .001$ ) and was maintained for at least 12 months after treatment discontinuation.

An observational study in 357 patients with acute and chronic tendinopathies also demonstrated that the efficacy of 28 days of local treatment with Traumeel ointment was comparable to that of diclofenac gel.<sup>15</sup> Improvements were observed in most patients after 3 to 7 days of treatment. Pain scores decreased by  $5.7 \pm 2$  and  $5.0 \pm 2.7$  in the Traumeel and diclofenac groups, respectively, and mobility scores also showed comparable improvements.

**Fibromyalgia.** In a single-center, double-blind study, a bioregulatory combination therapy comprising Traumeel, Spascupreel, Graphites Homacord, Cerebrum compositum, and Thalamus compositum was compared with placebo (saline) in 20 patients with clinically diagnosed fibromyalgia.<sup>16</sup> The bioregulatory combination therapy was administered by twice-weekly mesoinjections over the trigger points sensitive to digital pressure. After 8 weeks, muscular pain at the painful points was significantly reduced, and psychological status was improved in patients receiving the bioregulatory combination therapy compared with placebo. Methods achieving the double-blind conditions were not described, and therefore the Jadad score was rated low (=1).

**Rheumatoid Arthritis.** The effect of Traumeel S drops on the number of regulatory T-cells (% of  $10^6$  T helper-cells) in patients with mild rheumatoid arthritis was investigated in an open-label, nonrandomized study.<sup>17</sup> The number of regulatory T-cells increased in seven patients (five patients showed a moderate increase, and two showed a large increase) and decreased in two patients. The findings of this pilot study in patients with rheumatoid arthritis suggest Traumeel has an immunomodulatory effect, which needs to be confirmed in a more rigorous randomized, controlled, clinical trial.

**Degenerative and Traumatic Musculoskeletal Complaints.** A large observational study reported the outcomes of 3241 patients with degenerative and traumatic musculoskeletal complaints, including arthrosis, myologenosis, sprains/distorsions, periarthropathia humeroscapularis, epicondylitis, and tendovaginitis, following treatment with Traumeel injections.<sup>18</sup> All patients received Traumeel injections during routine clinical practice for periods ranging from less than 1 week to more than 6 months. Physicians rated the efficacy of Traumeel as “good” or “very good” in 78.8% of patients and reported that only 3.5% of cases showed no improvement.

Another large observational study in 1359 outpatients also reported the efficacy of Traumeel S tablets and drops to be “good” or “very good” in the treatment of injuries and inflammatory conditions in 80% of patients.<sup>19</sup>

#### Efficacy in Nonregistered Indications

**Chemotherapy-induced Mucositis.** Traumeel demonstrated significant benefits to patients with stomatitis undergoing allogeneic (n = 16) or autologous (n = 16) stem cell transplantation, as assessed by the World Health Organization (WHO) stomatitis score.<sup>20</sup> In this study, patients were randomized to 5 x 1 ampoule/day of Traumeel injection administered as a mouth rinse (n = 17) or

**TABLE 4** Overview of Randomized and Nonrandomized Clinical Studies of Different Applications of Traumeel

Study Reference	n	Indication	Control Group
Randomized studies			
Boehmer et al 1992 <sup>5</sup>	102	Acute sport injuries	Placebo (ointment base)
Zell et al 1988 <sup>5</sup>	73	Ankle sprains (sports-related)	Placebo (ointment base)
Thiel et al 1991 <sup>11</sup>	73	Hemarthrosis	Placebo
Ecocheaga et al 2004 <sup>16</sup>	20	Fibromyalgia	Placebo
Oberbaum et al 2001 <sup>20</sup>	32	Chemotherapy-induced mucositis	Placebo
Matusiewicz et al 1996 <sup>22</sup>	103	Corticosteroid-dependent asthma bronchiale	Placebo
Nonrandomized studies			
Kunt 1983 <sup>12</sup>	37	Hemarthrosis and/or hydrarthrosis of a joint	Placebo
Präg 2004 <sup>14</sup>	211	Tendinosis	Thermotherapy (Hydrosun), thermotherapy plus Traumeel
Timmermann et al 1998 <sup>52</sup>	236	Lumbar syndrome	Hydrocortisone; hydrocortisone plus Traumeel
Birnesser et al 2004 <sup>13</sup>	184	Epicondylitis	NSAIDs (mainly diclofenac)
Heine et al 2002 <sup>17</sup>	10	Rheumatoid arthritis	No control group
Geiger 1968 <sup>8</sup>	75	Posttraumatic soft tissue contusions and fractures	Conventional treatment
Mergen 1983 <sup>9</sup>	26	Posttraumatic soft tissue contusions and fractures	Traumeel ointment plus two doses of Traumeel drops
Thiel 1987 <sup>53</sup>	50	Supination-distortion trauma	Galvanic electricity
Oberbaum et al 1998 <sup>21</sup>	27	Chemotherapy-induced mucositis	No special treatment
Konca et al 1997 <sup>24</sup>	80	Tonsillectomy, postoperative course	Standard treatment
Matusiewicz et al 1997 <sup>23</sup>	50	Corticosteroid-dependent asthma bronchiale	Placebo
Singer et al 2007 <sup>54</sup>	30	Postoperative pain	No special treatment
Grudyanov et al 2006 <sup>55</sup>	141	Inflammatory periodontal disease	Conventional therapy
Grudyanov et al 2007 <sup>56</sup>	112	Inflammatory periodontal disease	Different Traumeel treatments
Ribot-Florit 2001 <sup>57</sup>	66	Dental extraction (symptom control)	Analgesics, NSAIDs
Ostazewska et al 1997 <sup>58</sup>	40	Postoperative complaints	Ointment monotherapy; ointment plus laser biostimulation; ointment plus laser biostimulation plus phonophoresis
Larentsova et al 2002 <sup>59</sup>	105	Peridontitis	Conventional treatment
Zilinskas 2002 <sup>60</sup>	42	Gingivitis, peridontitis	Laser scalar plus chlorhexidine
Diaz et al 1998 <sup>61</sup>	78	Dental root canal treatment	Standard treatment
*Only 5 compounds; NSAIDs indicates nonsteroidal antiinflammatory drugs.			



TABLE 4, continued

Galenic Form	Jadad Score	Outcome
Ointment (Traumeel Sine)*	4	Significant reduction of circumference with Traumeel Sine vs placebo ( $P=.028$ )
Ointment	4	Day-time joint mobility significantly improved ( $P=.005$ ) Pain on motion significantly improved at day 10 ( $P<.0001$ )
Injection solution	1	Superior joint mobility and pain relief, and lower effusion volume in Traumeel group
Injection solution	1	Pre- and posttreatment comparison showed improvements in muscular pain and pain in painful joints
Ampoules as a mouth rinse	4	Significantly reduced stomatitis score ( $P<.01$ ) and fewer case of stomatitis and worsening
Injection solution	3	Pre- and posttreatment comparisons showed improvement of spirometric parameters, granulocyte migration, IgE, and steroid demand in the verum group
Injection solution	—	No detectable recurrence of effusions in the Traumeel group compared to recurrences in most control patients
Injection solution	—	Traumeel was more effective than Hydrosun
Injection solution	—	Traumeel monotherapy and in combination with hydrocortisone can be effective
Injection solution	—	Proof of noninferiority of Traumeel compared to NSAIDs
Drops	—	Immunomodulating effect on regulatory T-cells lymphocytes
Drops	—	Most patients were successfully treated within 5 days. Traumeel 3 x 30 drops/d were more effective than 3 x 10 drops/d
Drops and ointment	—	Higher dose of Traumeel (3 x 15 drops/d) more effective than lower dose (3 x 10 drops/d)
Ointment	—	Traumeel ointment more effective than galvanic electricity
Injection solutions as a mouth rinse	—	Traumeel reduced the duration of mucositis symptoms
Injection solution	—	Traumeel improved postoperative recovery (earlier mouth opening and acceptance of food) vs standard care
Injection solution plus Engystol	—	Remarkable reduction of steroid demand with Traumeel
Injection solution only; injection solution followed by oral treatment	—	Lower consumption of analgesics in patients treated with Traumeel (injection with or without oral treatment)
Tablets; injections solution; Engystol	—	Slightly positive effect of Traumeel compared to conventional therapy Engystol® had a more rapid effect than Traumeel
Tablets; injection solution; ointment; injection solution as mouth wash	—	Comparable efficacy of the different Traumeel application forms
Tablets	—	Reduction of pain, inflammation, and hemorrhage with Traumeel
Ointment	—	Traumeel ointment was useful in the treatment of postoperative complications
Ointment; ointment plus mexidol	—	Long-term stabilization of the pathological process with Traumeel
Ointment plus laser scalar	—	Effective disease stabilization with Traumeel
Ointment	—	Fewer foci and absence of pain in the Traumeel group

to placebo (solution without active components; n = 15) for 4 weeks. Immediate pain relief was reported after Traumeel administration. The WHO stomatitis score was significantly lower in patients receiving Traumeel than in those receiving placebo (10.4 vs 24.3;  $P < .01$ ). The development (66% vs 93%, respectively) and worsening (47% vs 93%, respectively) of stomatitis also occurred less frequently in the Traumeel group than in the placebo group. The methodology of this study was well reported, but the randomization procedure was not adequately described (Jadad score = 4).

A nonrandomized study in 27 patients with chemotherapy-induced stomatitis showed a reduction in the duration of symptoms of mucositis in patients receiving Traumeel S injection as a mouth rinse compared to standard treatment.<sup>21</sup> Traumeel also resulted in rapid pain relief, occurring between 20 minutes and 2.5 hours after treatment.

**Corticosteroid-dependent Asthma Bronchiale.** In a randomized, controlled study, patients with corticosteroid-dependent asthma bronchiale of more than 5 years duration and treated with 4 to 8 mg/day of triamcinolon were found to benefit from treatment with Traumeel.<sup>22</sup> Patients were treated with Traumeel injection (Traumeel S, 1 ampoule every 5 to 7 days for 20 weeks; n = 71) or placebo (n = 32) in addition to basic treatment with cortisone and methylxanthine. When compared to baseline, spirometry results were improved and immunoglobulin (Ig) E levels were decreased in the Traumeel group. Moreover, while steroid demand was increased in placebo-treated patients, demand was reduced in patients receiving Traumeel. Shortcomings regarding the reporting of the study randomization and double-blind procedures resulted in a Jadad score of 3.

In a nonrandomized study, patients with severe corticosteroid-dependent asthma bronchiale (n = 50) were allocated to one of two groups: to receive standard treatment with steroid/methotrexate or standard treatment with steroid/cyclosporine.<sup>23</sup> Patients in each of these groups were then allocated to additionally receive Traumeel S injection plus Engystol N or placebo or no further treatment. This study suggested that the combination of Traumeel and Engystol may provide relief for patients with asthma bronchiale, as the greatest reduction in steroid demand was observed in patients also receiving this combination therapy.

**Tonsillectomy (Postoperative Treatment).** In a study of 80 patients with purulent tonsillitis, Traumeel S injection (1 ampoule/day intramuscularly; n = 40) or standard treatment (n = 40) was given after surgery.<sup>24</sup> After 5 days, patients receiving Traumeel S reported a significantly greater improvement in pain, as assessed using a VAS pain scale than patients on standard treatment ( $P = .04$ ). Patients given Traumeel also found it easier to open their mouths the day after surgery and accepted food earlier than did placebo-treated patients.

### Constituents of Traumeel

Indications for the use of the constituents of Traumeel in phytotherapy and in micro- and ultra low dilutions are presented in Table 5.

***Aconitum napellus* (Aconite).** *Aconitum napellus* root has been widely used in traditional Asian medicine as a treatment for rheumatism and wounds, but it is not popular in modern Western phytotherapy. A prescription of *Aconitum* in micro- and ultra low dilutions is given in cases of violence and where sudden stress causes intense anguish. Signs attributed to *Aconitum* are erythema of the face, heat, flushing, and fever.

Analgesic effects of *Aconitum napellus* have been demonstrated in preclinical models.<sup>25</sup> In a double-blind, placebo-controlled clinical trial, microdilutions of *Aconitum* relieved postoperative pain and agitation in children.<sup>26</sup>

***Arnica montana* (Arnica).** *Arnica montana* is very popular in modern phytotherapy due to its analgesic, antibacterial, and antiinflammatory properties. The extracts are used for the topical treatment of a wide range of rheumatic conditions. The active ingredients are flavonoids, glycosides, and lactones. Micro- and ultra low dilutions of *Arnica* are indicated for the treatment of trauma and its associated symptoms, such as pain, swelling, and bruising. Specific assessments have confirmed the safety of microdiluted *Arnica* preparations.

Pooled results from double-blind, placebo-controlled studies suggested that treatment with *Arnica* C30 resulted in a greater reduction of muscle soreness immediately after a marathon run than placebo.<sup>27</sup> Information is not available on the superiority of one potency of *Arnica* to another. A review of all prospective, controlled trials investigating microdilutions of *Arnica* (68 comparisons in 49 clinical trials) observed significant treatment effects in patients with traumatic injuries in a random effect meta-analysis but not in meta-regression models.<sup>28</sup> The heterogeneity of the results might be a consequence of the inclusion of trials investigating *Arnica* as monotherapy and as an ingredient in complex preparations (ie, in combination with other ultra low–diluted remedies). Complex remedies contributed mainly to the positive assessment of *Arnica* in the random effect meta-analysis.

Ultra low dilutions of *Arnica* D6 have been shown to improve recovery after bilateral endoscopic carpal-tunnel release, significantly reducing pain compared with placebo.<sup>29</sup> Furthermore, a randomized, double-blind, placebo-controlled study in patients with varicose vein surgery (n = 60) showed a trend towards a beneficial effect of *Arnica* D12, in terms of reductions in postoperative hematoma and pain.<sup>30</sup> *Arnica* D30 treatment also resulted in a significantly larger reduction in pain score compared to placebo after tonsillectomy (n = 111).<sup>31</sup> In combination with ultra low dilutions of *Hypericum*, ultra low dilutions of *Arnica* were particularly effective in patients with dental-associated interventions and neuralgia.<sup>28,32</sup>

***Atropa belladonna* (Belladonna).** Due to toxicity, *A belladonna* extracts are not used in modern phytotherapy. In micro- and ultra low dilutions, *A belladonna* is indicated in the treatment of complaints with sudden onset and disappearance; in pain described as throbbing, sharp, cutting, shooting or burning; and in bright red or inflamed parts with intense burning or hyperesthesia. Ultra low dilutions of *A belladonna* are

**TABLE 5** Indications of Traumeel Constituents in Phytotherapy and in Micro- and Ultra Low Dilutions

Constituents	Phytotherapy	Micro- and Ultra Low Dilutions	Important Results From Clinical Studies With Micro- and Ultra Low Dilutions
<i>Aconitum</i>	Not used	Postoperative pain, analgesia	Relief of postoperative pain and agitation in children (double-blind, placebo-controlled study) <sup>26</sup>
<i>Arnica</i>	Topical treatment for rheumatic conditions	Trauma and trauma-associated symptoms	Lower muscle soreness with <i>Arnica</i> C30 (pooled results) <sup>27</sup> Less pain after tonsillectomy ( <i>Arnica</i> D30) <sup>31</sup>
<i>Belladonna</i>	Not used due to toxicity	Acute conditions characterized by inflammation and infection	Effective in acute dermatitis during radiotherapy for breast cancer <sup>33</sup> Significant reduction if migraine attacks (in combinations with other ultra low-diluted drugs) <sup>34</sup> Reduced frequency of recurrence of otitis media in pediatric patients <sup>35</sup>
<i>Bellis perennis</i>	Not established	Deep bruising, complaints after physical trauma, symptoms associated with rheumatism, hematoma	Reduction of postpartum bleedings (in combination with <i>Arnica</i> ; a placebo-controlled study) <sup>36</sup>
<i>Calendula</i>	Ecze-ma, conjunctivitis, thrush infections, minor injuries, skin problems	Internal and external injuries where the skin is broken	Prevention of radiotherapy-related dermatitis (topical ointment; open comparison with tromaline, phytotherapeutic extract) <sup>37</sup> Greater reduction of ulcer surface (topical phytotherapeutic extract) <sup>38</sup>
<i>Chamomilla</i>	External use for wounds, sunburn, burn, hemorrhoids, mastitis, leg ulcers Internal use for nervous digestive upsets, insomnia, travel sickness	Sensitivity to every perception (eg, surroundings, people, pain)	Anti-inflammatory effect was superior to placebo (ointment vs ointment base; phytotherapeutic extract) <sup>39</sup> More rapid decrease of weeping wound area (phytotherapeutic extract) <sup>40</sup>
<i>Echinacea</i>	Internal use for infections, early stages of cough and cold External use for herpes, acne, infected injuries	Similar indications as in phytotherapy	Significant decrease of symptoms of sinusitis (combined with other remedies in ultra low dilutions; compared to placebo) <sup>41</sup>
<i>Hamamelis</i>	Topical treatment for minor skin lesions, local skin inflammations, hemorrhoids, varicose veins	Venous bleeding, venous and varicose disorders	Noninferiority to bufexamac in atopic dermatitis (phytotherapeutic extract) <sup>42</sup> Reduction of cutaneous blood flow <sup>43</sup>
<i>Hepar sulfuris</i>	Not used	Inflammation, purulent processes after the highly acute phase	Monotherapy not investigated in clinical trials
<i>Hypericum</i>	Internal use for depressive mood disorders External use for wounds, burns, dermatitis, myalgia	Similar indications as in phytotherapy	Anti-inflammatory (analgesic properties): improvement of eczematous lesions in patients with subacute dermatitis (phytotherapeutic extract) <sup>45</sup>
<i>Mercurius solubilis</i>	Not used	Infectious diseases of mouth and throat, edema, inflammation	Shorter duration of fever and fewer recurrences of otitis media in children <sup>35</sup>
<i>Millefolium</i>	Injuries, wounds	Cases with bright red bleeding	Not performed
<i>Symphytum</i>	Ulcers, colitis, rheumatism, psoriasis, eczema, injuries	Bone injuries, bone fractures (acceleration of callus formation)	Not investigated in micro- or ultra low dilutions

predominantly prescribed in acute conditions characterized by inflammation and infection.

Prospective clinical studies have investigated the efficacy of various ultra low dilutions of *A belladonna* in patients with acute radiodermatitis during radiotherapy for breast cancer, with migraine, and in children with acute otitis media. The double-blind trial in patients with acute radiodermatitis showed a trend towards greater efficacy of *A belladonna* 7CH compared to placebo, as assessed by a calculated severity index (the sum of the scores of four parameters, including breast skin color, warmth, swelling, and pigmentation).<sup>33</sup> The double-blind, placebo-controlled treatment of 60 patients with migraine with one or two of eight ultra low-diluted ingredients (*A belladonna*, *Ignatia*, *Lachesis*, *Silicea*, *Gelsemium*, *Cyclamen*, *Natrium muriaticum*, and *Sulphur*) resulted in a significant reduction of the periodicity, frequency, and duration of migraine attacks.<sup>34</sup> Additionally, a prospective comparison between several ultra low-diluted remedies as monotherapy (*Aconitum*, *Belladonna*, *Chamomilla*, *Mercurius solubilis*, *Pulsatilla*, *Silicea*; n=103) and conventional therapy (n=28) showed a reduced frequency of recurrence of acute otitis media in pediatric patients.<sup>35</sup>

***Bellis perennis* (Daisy).** *Bellis perennis* extract, traditionally used as a topical treatment for wounds, is not established in modern phytotherapy. In ultra low dilutions, *Bellis perennis* is used for the treatment of deep bruising, complaints after physical trauma, rheumatism-associated symptoms following overexertion, hematoma, hemorrhage, and venous stasis.

A randomized, double-blind study compared the effects of ultra low dilutions of *Arnica* (10<sup>6</sup>) and *Bellis* (10<sup>60</sup>) with placebo in 45 patients with mild postpartum bleeding.<sup>36</sup> The mean baseline hemoglobin level was 12.7 g/dL in all treatment groups. Seventy-two hours postpartum, there was a greater reduction in the mean hemoglobin level of patients in the placebo group compared with patients in the two active treatments groups (11.6 g/dL vs 12.4 g/dL, respectively; *P* < .05).

***Calendula officinalis* (Marigold).** *Calendula* extracts are used externally for the treatment of eczema, conjunctivitis, thrush infections, minor injuries, and skin problems. Ultra low dilutions of *Calendula* are commonly used for the treatment of internally and externally injuries with skin damage.

A randomized, open-label, phase III trial presented preliminary evidence for *Calendula* ointment in the prevention of radiotherapy-related dermatitis.<sup>37</sup> Fewer patients using *Calendula* reported grade 2 to 3 skin toxicity compared to the control group using tromaline (41% vs 63%, respectively; *P* < .001). Additionally, a placebo-controlled trial in 34 patients with lower leg venous ulcers reported a mean reduction in ulcer surface area in 41.7% of patients using *Calendula* ointment compared to 14.5% in the control group.<sup>38</sup> Complete epithelialization of the ulcer area was observed in seven patients using *Calendula* vs four controls.

***Chamomilla* (Spec) (Chamomile).** In phytotherapy, *Chamomilla* is used externally for wounds, sunburn, burns, hemorrhoids, mastitis, and leg ulcers, and is taken internally for nervous digestive upsets, insomnia, and travel sickness. Ultra low

*Chamomilla* dilutions are indicated in patients who are sensitive to all things and sensations, such as to their surroundings, people, and pain.

In healthy volunteers with experimentally induced skin lesions, an ointment containing a 2% ethanol chamomile flower extract was reported to have a superior antiinflammatory effect compared to the ointment base alone.<sup>39</sup> A placebo-controlled, double-blind trial investigating the effect of an ethanol *Chamomilla* fluid extract was also conducted in 14 patients after dermabrasion. Cessation of weeping and complete drying of the wound occurred more rapidly in *Chamomilla*-treated patients compared to placebo (15.0 ± 5.1 days vs 17.1 ± 5.5 days, respectively).<sup>40</sup> There was no evidence that microdiluted *Chamomilla* as monotherapy had been investigated in clinical studies.

***Echinacea* (*angustifolia* and *purpurea*) (Purple coneflower).** *Echinacea* stimulates the immune system and has antiviral and antibacterial effects. In phytotherapy, *Echinacea purpurea* is taken internally for infections and early stages of coughs and colds. External preparations are used for conditions such as herpes, acne, and infected injuries. In ultra low dilutions, *E purpurea*, *E angustifolia*, and *E pallida* are used for the same indications as *E purpurea* in phytotherapy.

Clinical interest in *Echinacea* focuses on its immunomodulatory effects, such as the prevention and treatment of upper respiratory tract infections. Most studies demonstrated the superiority of *Echinacea* phytotherapy in the prevention and treatment of respiratory tract infections compared with placebo. Microdiluted *Echinacea* D1 in combination with other microdiluted remedies, including *Cinnabaris* D4, *Hydrastis* D1, and *Kalium bichromatum*, resulted in a significantly greater decrease in the sum score of five symptoms of sinusitis compared with placebo (-6.2 vs -1.7, respectively; *P* < .0001).<sup>41</sup>

***Hamamelis virginiana* (Witch Hazel).** Extract of *Hamamelis* is used topically for the symptomatic treatment of minor skin lesions, local skin inflammations, hemorrhoids, and varicose veins. *Hamamelis* at low potencies (D2) or as the mother tincture is used for treating venous bleeding and venous and varicose disorders.

In a randomized, double-blind study, no significant differences were observed in the outcomes of 22 patients with atopic dermatitis treated with standardized *Hamamelis* extract compared with bufexamac ointment.<sup>42</sup> The study drugs were administered simultaneously on both forearms of each patient, with the side for each treatment randomly selected. Independent of treatment, there was a clear improvement in symptoms. Other clinical investigations demonstrated that *Hamamelis* treatment reduced cutaneous blood flow, skin temperature, and ultraviolet-induced erythema.<sup>43</sup>

***Hepar sulfuris* (*Hepar sulfuris calcareum*) (Calcium sulfurat Hahnemanni).** Samuel Hahnemann developed the use of micro- and ultra low dilutions of *Hepar sulfuris* mainly for the treatment of local inflammation and purulent conditions after the acute phase.

No clinical trials of *Hepar sulfuris* monotherapy were found in the literature search. As part of complex ultra low-diluted

remedies, *Hepar sulfuris* is effective at all stages of the inflammatory process, and it is particularly recommended for infectious diseases of the mouth and throat.

***Hypericum perforatum* (St John's Wort).** *Hypericum* extracts are commonly used for the treatment of functional depressive mood disorders. Topical preparations are used for the treatment of superficial wounds, burns, dermatitis, and myalgia. Ultra low dilutions of *Hypericum* are used for similar conditions. Symptoms indicating the use of *Hypericum* are head congestion with irritation of the nervous system and wounds that are very sensitive to touch.

Clinical studies investigating the antiinflammatory and analgesic properties of *Hypericum* were reviewed only. In a double-blind study of 21 patients with subacute dermatitis, significantly greater improvement was observed in eczematous lesions following treatment with a cream containing *Hypericum* extract than after placebo (cream vehicle;  $P < .05$ ).<sup>44</sup>

***Mercurius solubilis Hahnemanni* (*Mercurius vivus*).** *Mercurius solubilis* was presented by Hahnemann to provide a soluble form of *Mercurius*. *Mercurius solubilis* is often used for the treatment of infectious diseases of the mouth and throat and is used in low potencies where the condition is characterized by edema and inflammation.

A prospective observational study comparing several single remedies in micro- and ultra low dilutions with placebo found that children with otitis media treated with *Mercurius solubilis* had a shorter duration of fever and fewer recurrences of otitis media in the following year.<sup>35</sup>

***Achillea millefolium* (Yarrow).** In traditional phytotherapy, *Achillea millefolium* is recommended for the treatment of injuries and wounds due to its antihemorrhagic, analgesic, and antiinflammatory properties. Clinical use in phytotherapy and in ultra low dilutions (recommended in cases with bright red bleeding) is based mainly on empirical evidence. Indications for the use of *Achillea millefolium* include traumas, injuries, gynecological complaints, circulatory disturbances, diaphoretic impairment, diseases of the urinary system, and functional intestinal complaints. No randomized, controlled clinical studies of *Achillea millefolium* were found in the literature search.

***Symphytum officinale* (Comfrey).** *Symphytum officinale* has been used in phytotherapy for the treatment of internal diseases, such as ulcers, colitis, and rheumatism, and of external diseases, including psoriasis, eczema, and injuries. Currently, it is commonly used in sports medicine, particularly for the treatment of injuries of the ankle. In ultra low dilutions, the remedy is mainly used for the treatment of bone injuries and bone fractures to accelerate callus formation and the healing of fractures.

## Safety

**General Side Effects.** Hypersensitivity reactions have been observed in isolated cases with all Traumeel presentations, and local allergic skin reactions have been reported with Traumeel ointment and/or gel. In rare cases, systemic treatment with Traumeel may be associated an increase in the production of saliva.

**Healthy Volunteers.** In an open-label study investigating the safety of Traumeel, 36 mild-to-moderate, transient adverse events were observed in 11 out of 20 healthy volunteers receiving Traumeel tablets (6 tablets/day).<sup>45</sup> The most frequently reported events were headache ( $n=15$ ), diarrhea and stomach discomfort/bloating ( $n=6$ ), and nausea ( $n=3$ ). No event was considered definitely or probably related to Traumeel, and all events resolved without special intervention despite continuation of treatment.

**Traumeel Injection Solution.** In a randomized, clinical trial in patients with chemotherapy-induced mucositis, the side effect profile of patients treated with Traumeel S injection differed from patients receiving placebo.<sup>20</sup> A greater frequency of graft vs host disease, sepsis, and gastrointestinal complications were reported for the Traumeel group, while more venous-occlusive diseases and pneumonia were reported for the placebo group. The small number of study participants and severity of their illness prevented any definitive conclusions regarding the safety of Traumeel S injection. The tolerability of Traumeel S injection was rated as "good" or "very good" in the majority of patients in two observational studies: one study was in 184 patients with epicondylitis, the other was in 3241 patients with different orthopedic indications.<sup>13,18</sup>

**Traumeel S Ointment.** A multicenter drug monitoring study including more than 3400 patients confirmed that Traumeel S ointment is well tolerated.<sup>10</sup> Adverse events, including transient local irritation or allergic skin reactions, were observed in 13 cases only. Treatment was discontinued in three patients due to allergic reactions.

**Surveillance Studies.** The safety of all marketed application forms of Traumeel was reviewed in a large survey of over 3.6 million patients.<sup>46</sup> Adverse events were observed in only 0.0035% of cases. Most adverse events were mild skin reactions after application of Traumeel ointment and pruritus at the injection site after Traumeel injection, both of which disappeared after treatment discontinuation.

**Comparisons With NSAIDs.** An observational nonrandomized study, demonstrated the superior tolerability of Traumeel S injections compared with NSAID injections in 184 patients with epicondylitis.<sup>13</sup> In this study, tolerability was rated as "very good" in 87.7% of patients receiving Traumeel and 44.9% of patients administered NSAIDs.

**Constituents of Traumeel.** No data regarding the safety of ultra low dilutions of the constituents as used in commercially available Traumeel presentations were found in the literature search. Reported safety issues were restricted to their presentations as used in phytotherapy.

## DISCUSSION

This review presents the available evidence for the clinical efficacy of the multicomponent combination medication, Traumeel, and its constituents in a broad range of indications including contusions, fractures, epicondylitis, musculoskeletal complaints, tendinosis, and tendinopathy. In addition, the review details the suggested bioregulatory, immunomodulatory,

and antiinflammatory mode of action of Traumeel and its constituents. Altogether, six randomized, controlled studies; 19 nonrandomized, controlled studies; four cohort studies; and numerous case reports support the clinical use of Traumeel in these indications, while several controlled studies provide evidence of the activity of the constituents of Traumeel in their key indications.

### Mode of Action

Efficacy in various clinical indications suggests that Traumeel works in a different way compared to NSAIDs. In contrast to NSAIDs, Traumeel and its constituents do not directly influence the metabolism of arachidonic acid but exert bioregulatory effects via the inhibition of various proinflammatory cytokines, such as Interleukin (IL)-2, IL-6, and tumor necrosis factor-alpha (TNF- $\alpha$ ); modulation of regulatory T-cells/transforming growth factor-beta (TGF- $\beta$ ); and inhibition of IL- $\beta$ , IL-8, and TNF- $\alpha$  production. The reviewed data suggest strong immunomodulatory effects in at least two important therapeutic target systems: the ECM and regulatory T-cells.

### Acute Sport Injuries

In current clinical practice, Traumeel ointment is commonly used for the treatment of physical trauma and sport injuries. Its efficacy in these indications is supported by investigations with several of the constituents of Traumeel, which demonstrate the immunomodulatory, antiinflammatory, and analgesic effects of *Arnica montana*, *Calendula officinalis*, and *Chamomilla*, and by the comprehensive clinical trial program of this multicomponent medication, which includes randomized and nonrandomized studies. Two well-conducted randomized, placebo-controlled studies (Jadad score = 4) demonstrated a greater reduction in swelling and pain and improved mobility in patients treated with Traumeel S ointment compared to patients receiving placebo.<sup>5,6</sup> Additional trials presented evidence of noninferiority of Traumeel compared with NSAIDs, including diclofenac.<sup>13,15</sup> Moreover, these findings are supported by a multicenter drug-monitoring trial of more than 3000 patients treated under conditions of everyday routine clinical practice.<sup>10</sup> Investigators reported the efficacy of Traumeel to be "good" or "very good" in more than 80% of patients.

The most likely explanation for Traumeel's efficacy in the treatment of physical trauma and sport injuries is through the induction of ECM remodeling and tissue repair. Cutaneous wound healing begins with an alternating keratinocytes-ECM interaction at the wound edge, where cells migrating into the area are exposed to dermal collagen. Ultimately, this process results in changes in the ECM and the development of a more favorable environment for cell migration.<sup>47</sup>

There is also evidence for the role of Traumeel in the modulation of growth factor activity, which, after injury, results in skeletal muscle regeneration. Regeneration is regulated by fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor, and TGF- $\beta$ , which have a major influence on

the reorganization of the cellular matrix. In models, TGF- $\beta$ 1 and TGF- $\beta$ 3, expressed by regenerating muscles during the first days after trauma, influence nearly all important processes for muscle regeneration.<sup>48</sup> These observations support the regulatory and immunomodulating effects of Traumeel during tissue regeneration after physical trauma and sport injuries. This theory is backed by preclinical studies suggesting that exogenous TGF- $\beta$  might promote the healing of acute and chronic wounds<sup>49</sup> and a phase II trial demonstrating a positive effect of topical TGF- $\beta$ 2 on diabetic foot ulcers.<sup>50</sup> Thus, improved TGF- $\beta$  signaling at least partly explains the efficacy of Traumeel in wound healing and tissue repair.

Findings of investigations regarding the constituents of Traumeel concur with those of the complete bioregulatory combination. *Arnica montana* reduced muscle soreness after a marathon run in a double-blind, placebo-controlled trial<sup>27</sup> and demonstrated a significant effect in patients with traumatic injuries in a meta-analysis.<sup>28</sup> Both *Calendula officinalis* and *Chamomilla* had effects on external injuries with skin damage, such as in radiotherapy-induced dermatitis (*Calendula*)<sup>27</sup> and dermabrasion (*Chamomilla*).<sup>40</sup> *Hepar sulfuris* and *Mercurius solubilis*, which are used mainly in multicomponent medications to increase the efficacy of the combination, might have broad antiinflammatory activity. Additionally, *Achillea millefolium* and *Symphytum officinale* have been used in traditional phytotherapy for the treatment of injuries and wounds, with *Symphytum officinale* being particularly commonly used in sports medicine.

Together, the evidence demonstrates the efficacy of Traumeel in the treatment of acute sport injuries, which may be attributed to its well-balanced composition of constituents.

### Hemarthrosis

Two placebo-controlled studies, one of which was randomized, support the use of intra-articular Traumeel injections in patients with hemarthrosis. The randomized study demonstrated the superiority of Traumeel injections on joint circumference and mobility, intensity of pain, and effusion volume vs placebo.<sup>11</sup> In the nonrandomized study, patients administered Traumeel injections showed a reduction of effusion compared to placebo and not one required a second aspiration.<sup>12</sup>

Several constituents of Traumeel have shown activity in bleeding-related disorders. *Bellis perennis* diminished postpartum bleeding in a double-blind, placebo-controlled study,<sup>36</sup> *Hamamelis* reduced cutaneous blood flow,<sup>43</sup> and *Arnica* D12 showed a trend towards a reduction of postoperative hematoma vs placebo.<sup>30</sup>

### Epicondylitis

Traumeel injections are at least as effective as NSAID injections in patients with epicondylitis; noninferiority on all evaluated variables was demonstrated by a well-conducted, nonrandomized multicenter study.<sup>13</sup> In this study, Traumeel was also significantly superior in relieving pain at rest and

improving joint mobility than NSAIDs. Global outcome as rated by patients was also more frequently rated as “good” or “very good” by the Traumeel group. These results suggest that Traumeel may be considered a valid alternative to NSAIDs for the symptomatic treatment of epicondylitis.

### **Tendinosis and Fibromyalgia**

While there is evidence for the efficacy of Traumeel in patients with tendinosis, the data are not definitive due to the nonrandomized nature of the two studies. One of these nonrandomized studies showed that, compared to thermotherapy, patients treated with Traumeel injections had significantly improved pain relief, which was maintained after treatment discontinuation.<sup>14</sup> The observational study reported comparable improvements in mobility scores between Traumeel ointment and diclofenac gel.<sup>15</sup>

For patients with fibromyalgia, findings of a small double-blind, placebo-controlled study investigating Traumeel in combination with other medications with bioregulatory properties delivered in micro- or ultra low doses are promising.<sup>16</sup> Patients benefited from significant reductions in muscular pain, although the results should be interpreted with caution due to few participating patients (n = 20) and methodical shortcomings (Jadad score = 1).

### **Rheumatoid Arthritis**

The efficacy of Traumeel in the treatment of rheumatoid arthritis was suggested in preclinical investigations, which demonstrated antiinflammatory effects ranging from the inhibition of proinflammatory cytokines, such as IL-2, IL-6, and TNF- $\alpha$ , to the modulation of regulatory T-cells. Results of an open-label, nonrandomized, pilot study in patients with rheumatoid arthritis support preclinical findings regarding the immunomodulatory action of Traumeel.<sup>17</sup> However, the observed changes in regulatory T-cells in patients were not unidirectional because increases as well as decreases were reported, all of which need to be confirmed in more rigorous and investigative clinical trials.

### **Chemotherapy-induced Mucositis**

The antiinflammatory and immunomodulatory effects of Traumeel in patients with chemotherapy-induced mucositis were demonstrated in a randomized, well-conducted study (Jadad score = 4)<sup>20</sup> and a nonrandomized study.<sup>21</sup> Efficacy in this indication might be explained by inhibition of proinflammatory cytokines (IL-1 and TNF- $\alpha$ ) at the start of mucositis, the tissue-protecting properties of some of the Traumeel constituents further in the course of the disorder, the antibacterial effects of some constituents during ulceration, and the bioregulatory effects supporting skin regeneration during healing.

### **Asthma Bronchiale**

Two studies investigated patients with corticosteroid-dependent asthma bronchiale, a severe atopic disorder charac-

terized by airway hyper-reactivity and airway remodeling as result of T helper (Th)-2 cell responses in the lung. Treatment with Traumeel was associated with a reduced demand for steroids and improved lung function.<sup>22,23</sup> These effects might reflect the induction of bioregulatory processes, such as the equalization of Th-1 cells, Th-2 cells, and regulatory T-cells and their responses. However, these results and the effects on T-cells need to be confirmed in further clinical studies.

### **Tonsillectomy (Postoperative Treatment)**

A controlled study demonstrated that recovery after tonsillectomy was improved when patients were administered Traumeel compared to standard treatment.<sup>24</sup> This observation is supported by several studies investigating the constituents of Traumeel, including *Arnica* D12 for postoperative pain,<sup>30</sup> *Arnica* D30 given posttonsillectomy, and *Aconitum napellus* in postoperative pain and agitation in children.<sup>26</sup>

### **Traumeel as an Alternative to NSAIDs**

Traumeel has been shown to be as equally as effective as NSAIDs in the treatment of patients with various sport-related injuries. In an observational study in patients with acute and chronic tendinopathies, the reduction in pain and improvement in mobility was comparable between the Traumeel and NSAID groups.<sup>15</sup> Similar results were also observed after local Traumeel S injections and intramuscular NSAID injections in patients with epicondylitis.<sup>13</sup> These observations were confirmed by a recently published double-blind study (not included in the analysis).<sup>51</sup> In this study, a significantly superior reduction in pain was reported for elite athletes with nontraumatic tendinous pain treated with Traumeel S ointment compared with diclofenac ointment and with placebo ointment.

### **Safety**

Despite the impact of Traumeel on various immunological processes, the available evidence from clinical studies demonstrates that this multicomponent combination medication is well tolerated. Spontaneous adverse event reporting during more than 60 years of Traumeel use in clinical practice suggest an excellent safety profile. There are no indications in which there is an increased risk of hypersensitivity or allergic reactions with therapy. Monotherapy with micro- and ultra low dilutions of all constituents have also proven to be well tolerated in clinical practice. Moreover, the tolerability of Traumeel, in terms of the number and frequency of adverse events, is reported to be significantly improved when compared with NSAIDs.<sup>13</sup>

### **CONCLUSIONS**

There is mounting evidence supporting the clinical efficacy of the bioregulatory drug, Traumeel, in the treatment of patients with acute or subacute musculoskeletal problems, such as trauma and sport injuries. The observed efficacy of Traumeel may be credited to the immunomodulatory, antiinflammatory, and analgesic effects provided by the well-balanced combination of its

constituents. Traumeel's efficacy and excellent safety profile warrant its consideration as a first-line treatment of physical trauma and sport injuries and as an alternative to NSAIDs.

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# Neurexan: The Bioregulatory Approach to the Treatment of Stress and Stress-related Disorders— Preclinical and Clinical Considerations

Dietrich Göthel, MD

In modern life, chronic stress becomes a main culprit of many mental and somatic disorders. The therapy for chronic stress often requires a multidisciplinary approach because drug therapies are often unsatisfactory and are associated with adverse effects that impair the possibilities of long-term treatment. In addition, recent research on stress and stress-related disorders revealed the high complexity of neurotransmitter physiology, implicating multiple possible targets for treatment. However, this complexity probably impairs the success of treatment with selectively acting pharmaceuticals that are developed to target specific metabolic pathways. Therefore, it is more and more apparent that regulating transmitter balance may be a promising extension of available treatments. Neurexan, a natural compound medicinal product, seems to be a potential therapeutic option. The medication has been studied in clinical trials and seems to be effective in the treatment of stress

and stress-related complaints, such as sleep disturbance, nervousness, restlessness, difficulties with concentration, forgetfulness, and nocturnal anxiety. In preclinical studies, an affinity of Neurexan to the central  $\gamma$ -aminobutyric acid (GABA) benzodiazepine receptor was observed. From these results, the peripheral benzodiazepine receptor system also could be a target of the medication, generating neuroactive steroids known to be highly potent allostatic modulators of the GABA signaling pathway. Both receptors are fundamentally involved in the mediation of the stress response. Based on the results from preclinical and clinical studies performed with Neurexan and knowledge about stress, this study will try to contribute to a better understanding of the potential implication of Neurexan in the treatment of stress and stress-related disorders. (*Altern Ther Health Med*. 2011;17(2 Suppl):S32-S40.)

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**F**rom an evolutionary viewpoint, stress is important for the development of successful strategies for animals and humans to cope with the demands of life. If an individual is able to meet the challenges of life, then acute stress seems not to be harmful and physiological balance can be maintained. However, if “overwhelming” tasks last too long, then stress becomes deleterious and increases an individual’s vulnerability to mental and somatic disorders. Based on this distinction, good stress is termed *eustress* and bad stress is termed *distress*. In modern life, work can become a source of distress for a variety of reasons. Feelings of inadequate control over one’s work, frustrated hopes and expectations, and losing life’s meaning seem to be independent causes of chronic exhaustion and can lead to so-called burnout. Nearly 30% of the adults in Western countries are affected by burnout.<sup>1,2</sup>

In recent years, research on stress has considerably enhanced the understanding of the underlying pathophysiology. Many mediators and neurotransmitters that are directly associated with the stress response can be identified. Examples include corticotropin-releasing factor, corticosteroids, oxytocin, prolactin and vasopressin, serotonin, norepinephrine, dopamine,

vasoactive intestinal polypeptide, neuropeptide Y, cholecystokinin, substance P, nitric oxide, proinflammatory mediators,  $\gamma$ -aminobutyric acid (GABA), and neuroactive steroids. These mediators and neurotransmitters play a key role in the overall balance between neuronal excitation and inhibition.<sup>3</sup>

Because of the complexity of the pathophysiology of stress, the focus on more or less selective pathophysiological targets, as is the case in treatment with benzodiazepines (eg, diazepam and lorazepam) and selective serotonin reuptake inhibitors (SSRIs; eg, citalopram, fluoxetine, and paroxetine), is often suboptimal with heterogeneous outcomes.<sup>4,5</sup>

Therefore, it is suggested that a multitarget bioregulatory approach may expand the existing treatment possibilities. Bioregulation aims at homeostasis that is “the coordinated physiological reaction which maintains most of the steady states in the body.”<sup>6</sup> This integrates the mind and the body, and it is assumed that nearly all naturopathic treatments affect the body holistically.<sup>7</sup> Complex homeopathic preparations seem to act both on a low substantial level and on an energetic level because of the succussion procedure of the diluted constituents during the manufacturing process. This may explain the observed modulating effect on homeostasis. Therefore, bioregulatory medicine seems to be especially useful in functional disorders of the mind and body.<sup>8</sup>

Neurexan, a complex homeopathic medicinal product, is effective in fostering mental balance during stress and associated complaints (eg, nervousness, restlessness, and sleeplessness). Based on the results of preclinical and clinical research on

Neurexan and knowledge about the pathophysiology of stress, this study will discuss the hypothetical mode of action of this medication and the possible clinical implications for the treatment of stress and stress-related disorders.

## STRESS AND STRESS-RELATED DISORDERS

From a scientific viewpoint, stress is generally described as a state of bodily or mental tension resulting from factors that tend to alter an existing equilibrium.<sup>9</sup> This definition can lead back to Hans Selye, who defined stress as “the non-specific response of the body to any demand” leading to perturbations of physiological and psychological homeostasis.<sup>10</sup> Selye observed that the body develops a nonspecific response to stressors when their action is prolonged. This was termed *general adaptation syndrome* and involved the following triphasic response<sup>11</sup>:

1. The “alarm reaction”: Acute stress is characterized by an activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system, with elevated levels of cortisol, epinephrine, and norepinephrine. The physiological adaptation (eg, an increase in blood pressure, heart and breathing rates, glucose level, and oxygen consumption) allows the body to act according to the archetypical “fight-and-flight” behavior. After a stressful event, a sufficient recovery restores the body to the basic level.
2. The “stage of resistance”: In the case of permanent stress with insufficient recovery from stressful events, the organism progressively loses the natural capacity to regulate stress response and to recover to the normal level again. Persistent changes of physiological parameters affected in acute stress cause a pathological adaptation in the attempt of the organism to obtain an optimal adaptation to chronic stress. Disorders, such as hypertension, metabolic syndrome, gastrointestinal dysfunction, and headache, develop.
3. The “stage of exhaustion”: In the case of persistent stress, the signs and symptoms of the alert and resistance phase become irreversible, characterized by the loss of acquired adaptation. Chronic mental and somatic diseases are the consequences. Impaired sleep, concentration, and memory and mood disorders become more and more prominent and are a characteristic feature of exhaustion and burnout.

From an evolutionary viewpoint, stressful situations should adapt the body to excessive physical demands (“fight-or-flight” response) that are necessary for survival. However, in modern life, both fight and flight are typically not options and no adequate demand for such physiological and metabolic adaptations exists. Therefore, chronic stress becomes deleterious. An example of the serious consequences of chronic stress is burnout syndrome. The term *burnout* was coined in 1974 by the psychoanalyst Herbert

Freudenberger and originally related to people working in highly engaged social jobs (eg, teachers, nurses, and physicians) with increased risk for chronic exhaustion and illness. Meanwhile, burnout can affect nearly all social groups irrespective of occupation. Burnout is mainly regarded as the result of chronic stress that has not been successfully treated.<sup>12</sup> The complete syndrome is an end stage of chronic distress.

In addition to the subjective feeling of excessive demands and exhaustion, chronic stress induces many objective comorbidities, such as a decline in memory and cognition and sleep disturbances.<sup>13</sup> In addition, chronic distress is a considerable risk factor for the development of anxiety and depressive disorders.<sup>14</sup> Stressful events often precede the onset of depression, and stress also has been associated with the severity of the illness.<sup>15</sup> In addition, recent depressive and anxious symptoms predict stress response in humans.<sup>16</sup> Thus, the connection between chronic stress, insomnia, and mental disorders has the feature of a vicious circle and can explain, at least in part, the development of burnout syndrome.

Clinically, burnout syndrome is characterized by emotional exhaustion, depersonalization, physical fatigue, and cognitive weariness. This is accompanied by reduced personal accomplishment and satisfaction in performance, a sense of inadequacy, memory problems, loss of social contacts, and depressed mood.<sup>12</sup> The risk for drug or alcohol dependency is increased, and the immunocompromised body is susceptible to infections and a proinflammatory state. Also, insomnia impairs recovery, leading to dramatic consequences for mental and somatic health. Patients are susceptible to major depression, cardiovascular or gastrointestinal diseases, and even cancer.<sup>17</sup> In half of the participants with job-related burnout, some depressive disorders can be determined. The risk of depressive disorders is greater when burnout is severe.<sup>1</sup>

Chronic stress and burnout are linked to ill health. Although virtually all organs are affected by the exposure to exhaustive stress, the cardiovascular, neuroendocrine, immunological, and gastrointestinal systems are the first to experience functional changes. In Japan, sudden death caused by occupational overload is called *karoshi* and is related to chronic stress and burnout.<sup>18</sup>

From a physiological viewpoint in the case of chronic stress, the body, little by little, loses the capability to regulate the stress response. This also means that, in times without an acute stressful event, the physiological balance (allostasis) is not recovered again. Therefore, chronic distress and burnout can be viewed as a long-lasting overactive stress system with a loss of self-regulation.<sup>13</sup> This loss of acquired adaptation provokes an allostatic load that can accelerate disease processes.

The term *allostatic load* was coined in 1993 by Bruce McEwen and Elliot Stellar as a multisystem summary indicator that refers to the physiological risk of chronic stress response.<sup>19</sup> Allostatic load comprises the following parameters indicative of being relevant disease mediators: cortisol, epinephrine and norepinephrine, dehydroepiandrosterone (DHEA) sulfate, waist-to-hip ratio, glycosylated hemoglobin, high-density lipoprotein,

total cholesterol to high-density lipoprotein ratio, systolic and diastolic blood pressures, tumor necrosis factor  $\alpha$ , C-reactive protein, fibrinogen, d-dimer (ie, decomposition product of fibrin), percentage of body fat, triglycerides, and glucose.<sup>20</sup> In addition, mental disorders often associated with chronic stress, such as depression, are related to chemical imbalances in the central nervous system (CNS) that constitute a special form of allostatic load.<sup>21</sup>

The loss of allostasis, with changes toward allostatic load, and the development of diseases involve a complex interaction of neural, neuroendocrine, and neuroendocrine-immune mechanisms, with dysbalanced HPA axis activation as a central mechanism. For stress regulation and treatment options, two targets are especially important: the GABAergic system, acting via GABA, and the peripheral benzodiazepine receptor (PBR) pathway, generating neuroactive steroids known to be highly potent allostatic modulators of the GABA signaling pathway.

### THERAPEUTIC TARGETS FOR THE TREATMENT OF STRESS AND STRESS-RELATED DISORDERS

The first target is GABA, the principal inhibitory neurotransmitter in the brain. It plays a key role in the overall balance between neuronal excitation and inhibition. In the mammalian brain, as many as one third of all synapses are GABAergic.<sup>22</sup> GABA is synthesized in presynaptic neurons and stored in synaptic vesicles. On neuronal activation, GABA is released into the synaptic cleft, where it activates postsynaptic GABA receptors and reduces the excitability of the neurons.<sup>22-24</sup>

Excessive GABAergic signaling results in sedation, whereas the mildest attenuation of GABAergic signaling results in arousal, anxiety, restlessness, and insomnia. Therefore, GABA is essentially involved in the regulation of sleep. Dysfunction also has been demonstrated in psychiatric disorders, such as anxiety and depression.<sup>25</sup> The GABAergic system is also considered one of the major neuronal mechanisms that underlies learning and memory.<sup>26</sup> The GABAergic system plays a central role in homeostasis during stress; the inhibitory role of GABA on the HPA axis is well established.<sup>27</sup> GABA is known to inhibit the release of corticotropin-releasing hormone from the hypothalamus, followed by reduced secretion of adrenocorticotropin from the pituitary gland and, subsequently, glucocorticoids from the adrenal gland.<sup>28,29</sup>

Normally, the HPA axis is under autoregulatory control, and an increase of cortisol will negatively affect feedback and dampen HPA axis activity.<sup>9</sup> Disruption of this homeostatic mechanism may play an etiopathogenic role in disorders related to stress and is often associated with increased adrenal glucocorticoid output.<sup>30</sup> Intensive stress and a prolonged increase in corticosterone levels attenuate GABAergic control because of altered GABA(A) benzodiazepine binding density.<sup>31</sup> This impairs the inhibitory activity of GABA on HPA axis activation and can deplete resources. Although acute stress causes hypercortisolism, long-standing strain on the HPA axis may lead to hypocortisolism.<sup>32</sup> Therefore, for cortisol levels, the clinical findings in burnout and stress-related disorders are often inconsistent. Elevations in the levels of circulating glucocorticoids are often seen in depressive disorders<sup>33</sup>; in patients with chronic exhaustive conditions, such as chronic fatigue syndrome and vital exhaustion, hypocortisolism is a prominent feature.<sup>34,35</sup>

Benzodiazepines are widely used in the treatment of stress and stress-related disorders. These medications target the central benzodiazepine receptor, which is a component of the GABA(A) receptor distinct from the GABA binding site.<sup>36</sup> Receptor agonists, such as benzodiazepines and some natural compounds, only potentiate the effects of GABA and cannot directly activate the receptor. They enhance the effect of GABA by lowering the concentration of GABA required to open the GABA(A) channel, thus augmenting its inhibitory effects.<sup>25</sup> Flumazenil, an antagonist at the GABA(A) benzodiazepine binding site, displaces benzodiazepines from this receptor and is clinically used to neutralize the sedative effects of these drugs. In receptor-binding studies, Neurexan could displace flumazenil from the receptor, suggesting that enhanced GABA signaling is a mode of action of this natural compound medication.<sup>37</sup> This could reconstitute the GABAergic control in the stress response.

Additional targets of Neurexan may be the modulation of neuroactive steroids. Neuroactive steroids serve as endogenous homeostatic mechanisms, restoring both normal GABAergic activity and HPA axis function after acute stress.<sup>38</sup> They are involved in various neurological disorders (eg, anxiety and mood disorders) and psychotic, childhood, eating, dementia, stress, and postpartum disorders.<sup>39,40</sup> Neuroactive steroids (eg, allopregnenolone) are pregnane steroids and are among the most potent allosteric modulators of the GABA(A) receptor. They are active in nanomolar concentrations<sup>41</sup> and play a role in the fine-tuning of CNS functioning by targeting the activity of GABAergic and glutamatergic transmissions.<sup>40</sup> Thus, both inhibitory (GABA) and excitatory (*N*-methyl-D-aspartate) receptor functions are modulated.<sup>42,43</sup>

Neuroactive steroids can be synthesized by PBR-dependent pathways.<sup>44,45</sup> This receptor was first described in 1977 as a binding site for the benzodiazepine diazepam in tissues outside the CNS.<sup>46</sup> Meanwhile, it is known that PBRs are also present in the brain and are found in almost all peripheral tissues. They are highly expressed in tissues involved in steroid synthesis, and their levels of expression in normal tissues are correlated with the amount of mitochondria in the cell.<sup>47</sup> The PBR binds cholesterol and mediates its transport from the outer to the inner mitochondrial membranes, where it is converted into pregnenolone and neuroactive steroids (eg, allopregnenolone and DHEA).<sup>48,49</sup> Neuroactive steroids can easily diffuse across the blood-brain barrier to modulate neural activity.<sup>39</sup> However, PBR ligand signaling also affects peripheral tissues. Peripheral benzodiazepine receptor binding sites are particularly dense in peripheral organs that are highly activated during stress, such as the adrenal gland and the heart. Based on the control of steroid synthesis, a compound or medication with affinity to PBR may improve regeneration and energy supply and offer tissue protection.<sup>50</sup>

Experimental results suggest that PBR plays an important role in physiological adaptation to stress, anxiety, and depression<sup>51</sup> and that PBR ligands could especially prevent psychiatric

disorders that arise from a stress-induced imbalance of CNS function.<sup>39</sup> Several stress systems, such as the HPA axis, the sympathetic nervous system, the renin-angiotensin axis, and the neuroendocrine-immune axis, seem to be regulated by PBR.<sup>52</sup> Mechanisms of action that may play a role are the control of steroid genesis, immunomodulation, and modulation of mitochondrial respiration.<sup>50,53</sup>

The ability of both exogenous and endogenous PBR ligands to regulate steroid production supports the view that this site may be integral to an organism's response to stress.<sup>54,55</sup> In addition to benzodiazepines, many endogenous (eg, cholesterol) and exogenous (eg, some flavonoids) natural compounds are known to exhibit affinity to PBRs.<sup>56</sup> In addition, flumazenil is also able to occupy the receptor and, like benzodiazepines, was shown to exert metabolic effects in peripheral tissues.<sup>57</sup> This led back to the affinity of the medications to PBR.<sup>58,59</sup> Because Neurexan was able to displace flumazenil in receptor-binding studies,<sup>37</sup> it seems probable that this medication also mediates part of its effects by binding to the PBR and neuroactive steroid signaling.

Medications acting directly as PBR ligands, such as benzodiazepines, induce the formation of neuroactive steroids, which are potent modulators of the GABA(A) receptor.<sup>60</sup> In contrast, SSRIs act, as part of their mode of action, on an enzyme of the neurosteroidogenic pathway.<sup>61</sup> Consequently, both treatments, recommended for the therapy of stress-related complaints, increase the neuroactive steroid level.<sup>62,63</sup> Natural PBR ligands that increase the levels of neuroactive steroids, with a better safety profile than conventional medications, would be a valuable therapeutic extension in indications for which coping with stress is required.

#### NEUREXAN: A BIOREGULATORY COMPLEX MEDICATION FOR THE TREATMENT OF STRESS

Neurexan is a complex homeopathic preparation that contains a combination of diluted components. The constituents are *Passiflora incarnata* (white sarsaparilla) D2, *Avena sativa* (common oats) D2, *Coffea arabica* (coffee tree) D12, and *Zincum isovalerianicum* (valerianate of zinc) D4.<sup>64</sup> All components are listed in the *German Homeopathic Pharmacopoeia*.<sup>65</sup> Neurexan is used for the treatment of stress-related disorders, such as nervousness and sleep disturbances. The recommended daily dose is one tablet taken three times. In cases of acute disorders, the administration of one tablet every 30 to 60 minutes is recommended for temporary symptomatic relief, up to a maximum of 12 tablets daily.

In an in vitro study, the affinity of Neurexan to different receptors (GABA[A], GABA[A]-benzodiazepine binding site, and serotonin transporter) was tested using established receptor-binding assays. The results revealed that Neurexan has an affinity to the GABA(A)-benzodiazepine binding site of the GABA receptor, displacing approximately 50% of flumazenil (a receptor antagonist used in receptor-binding studies). (On the GABA receptor, half the maximal inhibitory concentration for a reconstituted formulation was 25 µg/mL.) The affinity to other receptors or enzymes tested (GABA[A], serotonin, and monoamine

oxidase A) was low and did not show significant binding. These data suggest that the clinical efficacy is at least partially mediated via the GABA(A)-benzodiazepine binding site.<sup>37</sup>

In a randomized, placebo-controlled, double-blind study, neurophysiological methods were used to determine the effects of Neurexan on psychophysiological condition. To investigate the effect of Neurexan during mental strain, healthy volunteers (N=30) were exposed to a stressful situation. For intraindividual comparison, a crossover design was used. After the administration of Neurexan (four tablets each) or placebo, participants of the study were exposed to a mental arithmetic stress test. The reward (financial compensation) was dependent on the test results, enhancing psychological pressure. During the test procedure, an electroencephalogram (EEG) was recorded. The psychological strains of the participants were assessed with the Profile of Mood States score. Under the treatment of Neurexan, the  $\alpha$ ,  $\beta$ , and  $\delta$  frequencies were modulated. Compared with the results after placebo administration, Neurexan significantly reduced the increase in the  $\alpha$  power caused by the circadian rhythm. Also, the increase of  $\beta$  waves during the mental stress test was significantly reduced after Neurexan administration ( $P < .05$ ). In addition, treatment with Neurexan caused a significant reduction of  $\delta$  waves compared with placebo. This may be indicative of a modulatory effect of the medication on the parasympathetic nervous system. When the Profile of Mood States subscores (ie, "displeasure," "drive," "fatigue," and "depressiveness") were examined, displeasure was more reduced in the verum group. The results of the arithmetic test showed no relevant difference between both treatments. Therefore, impairment of mental power after the administration of Neurexan can be excluded. In conclusion, the reduced power of the  $\beta$  waves during the stress test can be interpreted as emotional stabilization as the result of treatment with Neurexan, indicating improvement in coping with stress.<sup>66</sup>

In an observational study, patients with sleep disturbances were allocated to therapy with Neurexan (n=156) or a commercial variety of valerian (n=164). The duration of therapy under study conditions was 28 days. The dosage schedule was set up by a physician. All patients in the Neurexan group received the regular dose of one to three tablets a day. In 22% of the population, additional tablets were taken at bedtime. Based on the sleep diaries of patients, sleep latency was comparably reduced from baseline by both treatments. However, the improvement in sleep duration was significantly in favor of Neurexan within the first 2 weeks of the study. The time to improvement was mostly in the range of 3 to 7 days. On day 28, the quality of sleep was comparably improved in both groups. However, significantly more patients reported lack of daytime fatigue with Neurexan than with valerian ( $P < .05$  for the comparison). In addition, a slight reduction in mean blood pressure was observed in both groups during therapy. The overall effectiveness was rated as "very high" or "high" in more than 80% of patients. Overall tolerance was excellent in both groups. The data suggest that Neurexan has a similar efficacy to valerian.<sup>67</sup>

In another noninterventional observational study, the effectiveness of Neurexan was compared with that of different valerian-based preparations for the treatment of nervousness and restlessness. The choice and doses of study therapies were at the respective physician's discretion. The planned treatment duration was 2 weeks. The assessment of efficacy was based on the ratings (from 0 [asymptomatic] to 3 [severe]) of a summary score and on subscores at the end of the study (eg, nervousness or restlessness, excitability or jitteriness, sleep disturbance, hyperactivity, fitful sleep, nocturnal anxiety, forgetfulness or difficulties with concentration, fatigue, listlessness, moroseness, gastrointestinal disturbance, headache or pressure, and overall disease severity). In the final evaluation, 777 patients (553 receiving Neurexan and 224 receiving valerian) were included. In the Neurexan group, 42.9% of the patients received more than three tablets a day, 49.6% of the patients were treated with three tablets, and only 6% received less than three tablets per day. When the clinical parameters were studied, an overall significant effect of Neurexan could be observed ( $P < .001$ ). Concomitant medications with psychotropic drugs were rare (0.5%-1.0%) and are not considered to have a relevant impact on the study results. The results suggest that Neurexan is an effective and well-tolerated treatment for conditions associated with nervousness and restlessness.<sup>68</sup>

## DISCUSSION

Neurexan has been authorized to be marketed for the treatment of stress-related disorders, such as nervousness and sleep disturbances. The mode of action of complex homeopathic medications is still debatable. Like the use of highly complex composed plant extracts in phytotherapy, complex homeopathic medications are also a multicomponent therapy, suggesting a multitargeted approach with both treatments. In addition, the results of preclinical findings from both ultra low-diluted homeopathic preparations and phytotherapeutic extracts (eg, *Passiflora* species) suggest that at the level of cellular signaling there are, at least in part, some similarities between the two treatment concepts (eg, GABA[A] benzodiazepine receptor signaling).<sup>37,69</sup> This could also be an explanation for the frequently observed comparability in the claimed clinical indications of plant-derived preparations in phytotherapy and homeopathy. Therefore, profiling of the single constituents of Neurexan might provide new insights into the possible mode of action of this medication.

### *Passiflora incarnata*: Possible Contributions to the Efficacy of Neurexan

In homeopathy and phytotherapy, *P. incarnata* is traditionally used for comparable indications (eg, insomnia, anxiety, restlessness, neuralgia, nervous tachycardia, and spasmodic disorders) and seems to be particularly useful for nervous disorders.<sup>70,71</sup>

These indications could be confirmed in animal studies<sup>72,73</sup> with drug extracts, thereby showing anxiolytic, sleep-inducing, and anticonvulsant activity. A reduction of the craving for alcohol and nicotine was also shown.<sup>74</sup> After short-term administration of

the extract, a selective effect on reducing anxiety without the unwanted adverse effect of sedation was observed.<sup>75</sup> The anxiolytic efficacy was also proved in a randomized, double-blind clinical study.<sup>76</sup>

One of the constituents of *Passiflora* extracts is chrysin, a compound that is a ligand of the benzodiazepine receptors, both central (competitive mechanism) and peripheral (mixed-type mechanism).<sup>73</sup> The mode of action of the extract at the central nervous level seems to be related to the GABAergic and opioid systems because the antagonists flumazenil and naloxone could suppress them. In addition to enhancement of GABAergic activity, attenuation of glutamatergic activity is discussed.<sup>77</sup> In comparison, Neurexan has a proven affinity to the GABA(A) benzodiazepine receptor. To our knowledge, the activity on the opioid and glutamatergic system has not been evaluated.

### *Avena sativa*: Possible Contributions to the Efficacy of Neurexan

In homeopathy, *A. sativa* is the best tonic for treating debility after exhaustive diseases. It is indicated in insomnia after worry and mental exertion and in patients when exhaustion aggravates insomnia. In addition, it is used in cases of addiction to help the patients overcome drug and alcohol abuse.<sup>71</sup> These indications correlate with use in traditional phytotherapy, and the latter was also seen in a small human study.<sup>78</sup> In animal studies, sedative, antiseizure, and antiaddiction (nicotine and morphine) activities were demonstrated.<sup>79</sup> Investigations on the mode of action in in vitro models are lacking. However, data from studies in animals and humans strongly suggest that the CNS is a target of the constituents of *A. sativa*.

### *Coffea arabica*: Possible Contributions to the Efficacy of Neurexan

In homeopathy, *C. arabica* (*Coffea cruda*) is specially indicated in conditions associated with nervousness and extreme sensitivity. This includes hyperactivity of the mind and body, sleeplessness, great nervous agitation and restlessness, neuralgia in various parts, intolerance of pain, nervous palpitations, and convulsions. The sleep is superficial, and the patients easily wake up with the slightest noise.<sup>71</sup> Results from animal studies performed with *C. cruda*, 30 L, also suggest that the diluted preparation modifies sleep pattern and increases sleep intensity. In the EEG, an enhancement in slow  $\delta$  activity was demonstrated by trend.<sup>80,81</sup>

Extracts from *Coffea* are not used in modern phytotherapy. However, the mode of action of caffeine is well understood. An important target of caffeine is the adenosine receptor, where it acts as a competent nonselective antagonist of adenosine A(1) and A(2A) receptors in the brain.<sup>82</sup> The promotion of wakefulness by caffeine was proposed to be mediated by antagonizing adenosine receptor function because, during prolonged intervals of wakefulness, the adenosine levels increase in the brain to promote sleep. Adenosine receptors in the brain modulate acetylcholine release and dopamine transmission. They affect many brain functions, such as behavioral arousal, EEG  $\delta$  power, and

sleep.<sup>83</sup> The modulation of EEG slow  $\delta$  activity by diluted *Coffea*<sup>80</sup> supports the view that homeopathic *Coffea* preparations can act via adenosine signaling pathways.

Neurexan contains *C arabica* in a higher dilution (D12) than the other constituents. Based on the principle of homeopathy *similia similibus curentur*, it can be suggested that *Coffea* as a more highly diluted remedy can exert clinically the opposite effect of substantial doses of *Coffea* extract or caffeine. This assumption is in agreement with the indications claimed for *Coffea* in homeopathy and the experience from therapy with more highly diluted *Coffea* preparations. The mode of action of such more highly diluted *Coffea* in part functionally resembles that of adenosine or adenosine agonists at the cerebral adenosine receptors, with reference to sleep-promoting, anxiolytic, and antidepressive properties. In contrast, it has been reported that caffeine, an adenosine antagonist, can worsen anxiety and psychosis in affected people and can cause these mood disorders in otherwise healthy people after high caffeine intake.<sup>84</sup> The possible impact of Neurexan on the adenosine signaling pathways should be addressed in further research.

#### ***Zincum isovalerianicum*: Possible Contributions to the Efficacy of Neurexan**

Neurexan contains *Z isovalerianicum* (D4). *Zincum valerianicum* or *Z isovalerianicum* is a synthetic compound prepared from zinc oxide and valeric acid, a short carbonic acid derived from *Valeriana officinalis*. However, the content of valeric acid does not correlate with the pharmacological effects of valerian. Therefore, it is expected that this zincum preparation resembles more zincum (metallicum) than valerian. The constituent is used in low dilutions, with the main indications being irritable sleep disturbances with “restless legs” and neuralgia.<sup>65</sup>

In homeopathy, *Z valerianicum* is a favorite medicine to treat hypochondria with groundless fear. Exhaustion, tiredness, and weakness associated with excitement and agitation are typical symptoms. Patients are oversensitive, nervous, and sleepless; they often exhibit fidgety feet. The results of a retrospective study<sup>85</sup> confirm the possible usefulness of this remedy in patients with restless legs syndrome. It is also recommended for the treatment of different painful afflictions, such as neuralgia,<sup>71</sup> which underlines its specific affinity to the brain and nerves. Because of the calming effect, homeopathic zincum is also called “metallic opium.” Although the patients experience drowsiness by day, they cannot sleep at night. The wake-sleep cycle is inverted.<sup>86</sup>

Zinc is extremely important for brain physiology and neurotransmitter balance.<sup>87,88</sup> For the possible mode of action of homeopathic remedies, it is suggested that ultra low-diluted compounds that are relevant for cellular biochemistry can stimulate the physiological functions and the cellular metabolism in tissues with a functional imbalance. Examples include sulfur, ferum, and endogenous cellular compounds (eg, Ubichinon and the Krebs cycle intermediate biocatalyst used in bioregulatory medicine).<sup>8</sup> From this viewpoint, the role of zinc in neurophysiology can add some aspects to the hypothetical mode of action of

ultra low-diluted zinc-containing compounds and can support the claimed indications of Neurexan.

In the CNS, zinc acts as a neuromodulator of both excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission and seems to have a considerable role in stress response.<sup>89</sup> Most zinc-enriched neurons are inhibitory (GABAergic), especially in the spinal cord, and a direct modulation of GABA receptors by zinc may occur.<sup>90</sup> This could be an explanation for the calming effect of homeopathic zinc preparations on the motoric activity of the lower extremities, as the clinical experience in patients with restless legs suggests.<sup>85</sup>

Studies in animals and humans demonstrated that zinc deficiency is associated with depression and that treatment with zinc leads to antidepressant-like activity, especially in combination with antidepressant medications.<sup>91</sup> In addition, anxiety, anhedonia, and lethargy are characteristic mood disorders in those with zinc deficiency and are often associated with depressive disorders.<sup>92</sup> Animal models suggest that a direct or indirect activation of adenosine receptors may contribute to the antidepressantlike effect of zinc.<sup>93</sup> From the hypothetical viewpoint, better use of zinc at the receptor site by homeopathic lower-diluted zinc preparations could complement the functional adenosine agonistic activity of more highly diluted *Coffea*. Such a coordinated stimulation of adenosine signaling could also contribute to the calming activity of Neurexan.

#### **Comparability of Neurexan and Valerian in Clinical Trials**

Neurexan has shown comparable efficacy in clinical trials with valerian<sup>67</sup> and valerian-based preparations,<sup>68</sup> although there seems to be a tendency for the superiority of Neurexan in the indications investigated.<sup>68</sup>

Valerian is recommended for the treatment of restlessness and insomnia. However, in experimental studies and clinical trials,<sup>94,95</sup> sedating properties of common valerian extract preparations were found only inconsistently. Several observations indicate the putative efficacy of valerian extracts in the treatment of anxiety and stress-related symptoms and also a diminished response to mental stress under laboratory conditions.<sup>96</sup> This suggests that the claimed sedating properties of valerian may be more related to the anxiolytic or antidepressant effects of the extracts. This could also apply to the sleep-promoting activity of Neurexan. However, preclinical studies with valerianic acid, a single compound of valerian extract, revealed considerable sedative effects (eg, a prolongation of pentobarbital-induced sleeping time in animals).<sup>97</sup> This could explain why, compared with Neurexan in the valerian group, a “hangover”-like effect was more often reported.<sup>67</sup>

#### **Neurexan: A Partial Agonist Acting Through a GABAergic “Bystander Reaction”**

Like Neurexan, valerian extract interacts with the benzodiazepine site of GABA(A) receptors in a manner consistent with the known in vivo effects.<sup>98</sup> However, Neurexan seems to have more features of a partial agonist at the receptor without a relevant

affinity to the  $\alpha$ 1-subunit, which is responsible for the sedative effects of the benzodiazepine or nonbenzodiazepine hypnotic agents that preferentially bind to the  $\alpha$ 1-receptors (eg, zaleplon [Sonata]). Partial agonists show only partial efficacy in relation to a full agonist. Therefore, they may be capable of enough potentiation of GABA to reduce anxiety but not enough to cause sedation or amnesia. Thus, they could prove to be anxiolytic but not sedative, with a markedly reduced risk of dependence and interaction with alcohol, which would have enormous potential clinical advantages.<sup>99</sup> By targeting the GABA(A) benzodiazepine receptor, Neurexan seems to act as an allosteric modulator and facilitate the binding of GABA at its receptor. This is comparable to a “GABAergic bystander reaction” because endogenous GABA is necessary for signaling. Several conventional psychotropic drugs have a direct action on the receptor responsible for the toxicity of these drugs.

The assumption that Neurexan has similarities with a partial agonist not occupying the GABA(A) receptor  $\alpha$ 1-subunit, is also clinically supported by the results of arithmetic stress tests. No decline in concentration has been found. In addition, also from the results of EEG studies, no sedative effect was recognizable after the administration of Neurexan. Changes in the EEG suggest that, in addition to GABA, other neurotransmitters are relevant for the mode of action of Neurexan (eg, serotonin).<sup>66</sup> Independent of the exact knowledge about the neurotransmitters involved, the changes in the EEG recordings suggest a more balanced mood under stressful conditions, without impairment of mental function after the administration of Neurexan. Moreover, a possible modulation of both the central receptor and the PBR by Neurexan could not only explain the clinical efficacy of the medication but could also imply an important perspective for a holistic therapeutic approach in the prophylaxis and treatment of stress and stress-related disorders. However, this expected efficacy needs to be confirmed in further basic research and scientific approaches.

Because of its clinical efficacy and convincing safety profile, Neurexan seems to be a valuable extension of the available therapeutic opportunities in the treatment of stress and stress-related disorders. Drug safety is as equally important as drug efficacy. In contrast to conventional medications, treatment with Neurexan is not associated with adverse effects. Therefore, Neurexan seems to expand the possibilities of treatment in patients with stress and stress-related disorders. However, prevention is better than cure. Therefore, at early signs of overloading, therapy with Neurexan should be started to avoid the development of burnout.

## CONCLUSIONS

The results from preclinical and clinical studies performed with Neurexan provide a convincing profile for the clinical application of this complex medication in stress and stress-related disorders, such as nervousness, restlessness, and sleep disturbances.

In the brain, GABA is the principal inhibitory neurotransmitter. By targeting the GABA(A) benzodiazepine receptor, Neurexan could attenuate one of the most important pathways

of stress response, the HPA axis. Normally, the HPA axis is delicately controlled by an autoregulatory feedback system. However, in cases of chronic stress, the body, little by little, loses the capacity to regulate the stress response. This means that in times without an acute stressful event, the normal level is not recovered again. Therefore, chronic stress and burnout can be viewed as a chronically overactive stress system with a loss of self-regulation. This loss of adaptation provokes an “allostatic load” (eg, elevated levels of cortisol, epinephrine, cholesterol, glucose, and proinflammatory mediators), all known to be relevant disease mediators. Therefore, chronic stress virtually affects the whole body and is a considerable risk factor for cardiovascular diseases, immune dysfunction, diabetes mellitus, and sexual disorders.

In addition to the affinity to the central-type GABA(A) benzodiazepine receptor, Neurexan probably also occupies the peripheral type of the benzodiazepine receptor. Ligands of the benzodiazepine receptor type stimulate the synthesis of neuroactive steroids, which are powerful modulators of the GABA(A) receptor function but also seem to protect peripheral tissues, such as the heart, from stress-induced damage. In addition, neuroactive steroids appear to be especially important in the pathophysiology and treatment of many psychiatric disorders, such as anxiety and depression. There is evidence that the PBR system serves as an endogenous homeostatic mechanism, restoring both normal GABAergic and HPA function in cases of acute and chronic stress.

Clinically, Neurexan seems to function as a partial agonist at the GABA(A) receptor because it lacks a direct sedative effect. This belief is supported by the results of arithmetic stress tests, in which no decline in concentration was found. In addition, from the results of EEG studies, no sedative effect was recognizable after the administration of Neurexan. Partial agonists reduce anxiety but do not cause sedation or amnesia. Therefore, it seems likely that the calming and sleep-promoting effects of Neurexan in stress can mainly lead back to a mood-stabilizing, anxiolytic, or possibly antidepressive effect. EEG recordings support this view, suggesting a more balanced mood under stressful conditions without impairment of mental function.

In conclusion, all preclinical and clinical data indicate that Neurexan is a valuable medication for the prophylaxis and treatment of stress and stress-related disorders.

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