Pain Medicine

Pain Medicine 2010; 11: 356–368
Wiley Periodicals, Inc.

# Safety and Efficacy of Dietary Agmatine Sulfate in Lumbar Disc-associated Radiculopathy. An Open-label, Dose-escalating Study Followed by a Randomized, Double-blind, Placebo-controlled Trial

**Ory Keynan, MD,* Yigal Mirovsky, MD,† Samuel Dekel, MD,* Varda H. Gilad, CRA,‡ and Gad M. Gilad, PhD‡**

Orthopedics Department B, *Tel Aviv Sourasky Medical Center and

†Assaf Harofeh Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

‡G & V Gilad Ltd, Tel Aviv, Israel

*Reprint requests to:* Gad M. Gilad, PhD, G & V Gilad Ltd, 7 Plugot Street, Tel Aviv 67639, Israel. Tel: 972-3-631-6502; Fax: 972-3-631-6502; E-mail: gmgilad@gmail.com.

**Competing interest and financial disclosure:** Gad M. Gilad and Varda H. Gilad are patent owners of products related to the present work and stockholders in G & V Gilad Ltd. Ory Keynan, Yigal Mirovsky, and Samuel Dekel received research support from Trimaco Medical Division Ltd. The study was supported in part by Trimaco Medical Division Ltd, Rehovot, Israel, and by G & V Gilad, Ltd, Tel Aviv, Israel.

## Abstract

**Objective. Agmatine, decarboxylated arginine, was shown in preclinical studies to exert efficacious neuroprotection by interacting with multiple molecular targets. This study was designed to ascertain safety and efficacy of dietary agmatine sulfate in herniated lumbar disc-associated radiculopathy.**

**Study Design. First, an open-label dose escalation study was performed to assess the safety and side-effects of agmatine sulfate. In the follow-up study, participants diagnosed with herniated lumbar disc-associated radiculopathy were randomly assigned to receive either placebo or agmatine sulfate in a double-blind fashion.**

**Methods. Participants in the first study were recruited consecutively into four cohorts who took the following escalating regimens: 1.335 g/day agmatine sulfate for 10 days, 2.670 g/day for 10 days, 3.560 g/day for 10 days, and 3.560 g/day for 21 days. Participants in the follow-up study were assigned to receive either placebo or agmatine sulfate, 2.670 g/day for 14 days. Primary outcome measures were pain using the visual analog scale, the McGill pain questionnaire and the Oswestry disability index, sensorimotor deficits, and health-related quality of life using the 36-item short form (SF-36) questionnaire. Secondary outcomes included other treatment options, and safety and tolerability assessment.**

**Results. Safety parameters were within normal values in all participants of the first study. Three participants in the highest dose cohort had mild-to-moderate diarrhea and mild nausea during treatment, which disappeared upon treatment cessation. No other events were observed. In the follow-up study, 51 participants were randomly enrolled in the agmatine group and 48 in the placebo. Continuous improvement of symptoms occurred in both groups, but was more pronounced in the agmatine (analyzed n = 31) as compared with the placebo group (n = 30). Expressed as percent of baseline values, significantly enhanced improvement in average pain measures and in quality of life scores occurred after treatment in the agmatine group (26.7% and 70.8%, respectively) as compared with placebo (6.0% [$P \leq 0.05$] and 20.0% [$P \leq 0.05$], respectively). No treatment-related adverse events were noted.**

**Conclusions. Dietary agmatine sulfate is safe and efficacious treatment for alleviating pain and improving quality of life in lumbar disc-associated radiculopathy.**

**Study Registration. ClinicalTrials.gov Protocol Registration System Identifier: NCT00405041.**

**Key Words. Agmatine; Clinical Trial; Dietary Ingredient; Spine; Back Pain; Sciatica**

## Introduction

Symptomatic lumbar intervertebral disc herniation is a widely prevalent syndrome affecting about 1–2% of the population, usually at the age of 30–50 (the prime working years); thus, leading to significant economic impact [1]. The symptoms, which include pain, numbness, tingling, and weakness of the leg (commonly termed "sciatica"), usually improve in as many as 70–80% of patients within 3 months with conservative treatment that includes rest, physical therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs) medication [2–5]. Still, the neurological symptoms remain a major reason for patient complaints and thus, an unmet clinical issue [6]. These neurological symptoms may be the result of mechanical pressure on nerve roots leading to local ischemia, inflammation, or nerve damage [7]. Such nerve damage, in turn, can result not only in degeneration of the peripheral axons [8], but may also lead to degeneration of the corresponding parent sensory nerve cells in the affected dorsal root ganglia and of motor neurons in the spinal cord [9–11], a situation that is common to other musculoskeletal deformities causing nerve compression. Therefore, treatments aimed at protecting the injured parent nerve cells (i.e., neuroprotective) and their damaged peripheral axons (termed here, axonoprotective), may prove beneficial.

Agmatine [$(NH_2(CH_2)_4NH_2C(NH=)NH$] is a ubiquitous naturally occurring molecule [12]. It is biosynthesized by decarboxylation of the amino acid arginine [12], thus known as decarboxylated arginine. Agmatine is found in low amounts in many a foodstuff derived from plants [12–16], fish [17,18], and animal products [17]. Additionally, intestinal microbial production of agmatine is considered a major source of systemic agmatine [19]. Animal studies demonstrate that agmatine sulfate, the commonly used salt of agmatine, is absorbed by the gastrointestinal tract and distributed in the body [20], and that it crosses the blood-brain barrier [21]. Of specific interest, is the substantial preclinical body of evidence demonstrating the beneficial effects of agmatine on the nervous system. These include neuroprotection [22–31], neuropathic pain-reducing effects [22,25], and anti-anxiety and anti-depressive effects [32,33]. Furthermore, while agmatine biosynthesis (by arginine decarboxylation) in the nervous system is normally very low, it is greatly increased following injury [34]. This might suggest a role for agmatine in repair and regenerative processes in the central nervous system (CNS).

Agmatine has been shown in preclinical experiments to interact with multiple molecular targets important for nervous system function. These include: 1) modulation of several neurotransmitter receptors and receptor ionophores (e.g., nicotine, NMDA, imidazoline, and alpha 2-adrenoceptors) [35–38]; 2) blockade of key ionic channels (e.g., ATP-sensitive K+ channels and voltage-gated Ca++ channels) [39,40]; 3) inhibition of nitric oxide (NO) synthase and thus, modulation of NO production [41–44]; 4) inhibition of protein ADP-ribosylation [45] and thus, interference with cell signalling; 5) inhibition of matrix metalloproteases [46], enzymes implicated in nerve cell death and neuropathic pain [47,48]; and 6) inhibition of advanced glycation end (AGE)-product formation, a process involved in the pathology of diabetes and neurodegenerative diseases [49,50].

If all of the above interactions were active in humans, agmatine would be a valuable therapeutic for neuropathic and neurodegenerative disorders. For this to be realized, the compound would have to be safe and well tolerated at doses necessary to achieve the desired effects. In the present study therefore, we sought to ascertain the safety, tolerability, and efficacy of dietary agmatine sulfate in alleviating symptoms of radiculopathy by conducting first an open-label dose escalation trial followed by a randomized, double-blind, placebo-controlled trial in patients with herniated lumbar disc-associated radiculopathy.

## Materials and Methods

### *Study Design*

An open-label, dose-escalating, nonrandomized (phase I) study was designed to assess the safety and tolerability of agmatine sulfate. The study included participants with lumbosacral spine degenerative pathologies associated with radiculopathy. The study was conducted during the period of March–December 2006, at Tel-Aviv Sourasky Medical Center, Israel and approved by the Institutional Review Board (Trial Number: 05-302) and by the Israel Ministry of Health National Review Board (Trial Number: 20050479).

The follow-up study was a randomized double-blind, placebo-controlled trial (RCT), conducted in two medical centers and designed to evaluate the therapeutic efficacy of agmatine sulfate, in patients with herniated lumbar disc-associated radiculopathy. Therapeutic efficacy was assessed by measuring pain-related symptoms and sensorimotor function, and by recording general health-related quality of life. Safety and tolerability were also monitored as secondary outcomes. The study was conducted during the period of October 2006–March 2008, and approved by the Institutional Review Boards of Tel-Aviv Sourasky Medical Center and Assaf Harofeh Medical Center (Trial Numbers: 06-203 and 107/6, respectively) and by the Israel Ministry of Health National Review Board (Trial Number: 20060409). Before starting patient recruitment, the study was registered with ClinicalTrials.gov Protocol Registration System (ClinicalTrials.gov Identifier: NCT00405041).

### *Patient Population*

Men and women 18–75 years old were considered for inclusion in the study if they were diagnosed with lumbar radicular pain with or without motor deficits caused by lumbar intervertebral disc herniation corresponding to their symptoms as confirmed by computerized tomography (CT) imaging, and 2–48 weeks symptom duration in the RCT; longer duration of lumbosacral-associated

radiculopathy was allowed in the open-label trial. Few patients were also diagnosed by magnetic resonance imaging. Exclusion criteria included any musculoskeletal (other than lumbosacral spine-related), neuromuscular or any other significant clinical, medical or surgical conditions, substance abuse, women who were pregnant or breast feeding, and participants in other clinical trials. All procedures were performed after participants had read, understood, signed and retained a signed copy of the Ethics Committee's approved informed consent form. Eligibility of consenting participants was determined within 1–5 days prior to beginning of treatment after medical history recording and comprehensive clinical examination and laboratory tests of blood samples to ensure inclusion/exclusion criteria.

*Study Interventions*

The initial choice of treatment regimen in the open-label study was based on animal experiments reporting the effective dose range and gastrointestinal absorption [20]. These indicated that an oral dose of agmatine sulfate between 1,250 and 7,500 mg/day for a 50–75 kg body weight would result in safe and effective blood concentrations in human. We therefore decided that a daily dose range of 1,335–3,560 mg/day for at least 3-week duration should be considered safe and effective for human use.

Based on results of the open-label study reported here, demonstrating the safety of agmatine sulfate, and considering the time course and duration of lumbar disc herniation-induced neurological symptoms, we decided that a 14-day course of 2.670 g/day oral agmatine sulfate should be a safe and efficacious regimen for the RCT. Agmatine sulfate, manufactured according to international standards (ISO 9001), was formulated as a sole active ingredient for encapsulation (445 mg per capsule) and packaged under cGMP (current good manufacturing practice) conditions in an accredited facility. This preparation remained stable for at least 2 years when stored in the dark at room temperature. Placebo consisted of identical capsules containing indigestible dietary fibers (400 mg per capsule), similarly packaged in identical containers.

*Treatment Assignment and Regimen*

In the open-label study, escalating doses and regimens were taken by 4 cohorts, which were recruited consecutively to the study as described in Table 1.

In the RCT, eligible participants were assigned to receive either placebo or agmatine sulfate in a randomized fashion. Randomization was computer-generated for each of the two study centers. The sequentially numbered identical containers containing either placebo or agmatine sulfate capsules were dispensed by the principal investigators in a double-blind fashion. The physician and the patient, as well as the study monitor were blinded to treatment assignment for the duration of the study. To ensure allocation concealment, the principal investigators and the study coordinator kept the randomization code in sealed envelopes for emergency use only (i.e., to be opened only in case of serious adverse event such as severe illness, hospitalization or death). The study monitor ascertained that envelopes remained sealed throughout the study. The randomization code was open by the study coordinator for data analysis only after patients ended the study, but the statistical data analyzer was also blinded to treatment allocation. Study regimen consisted of six capsules daily (two in the morning, two at noontime, and two in the evening after meals) for 14 days.

**Table 1** Detailed treatment regimen and number of participants in the consecutive cohorts of the open-label study

| Cohort | No. of participants | Agmatine Sulfate Treatment Regimen |
|---|---|---|
| 1st | 5 | 1 capsule 3 times daily (1.335 g/day) for 10 days |
| 2nd | 5 | 2 capsules 3 times daily (2.670 g/day) for 10 days |
| 3rd | 12 | 8 daily capsules (2 in the morning, 3 at noontime and 3 in the evening) (3.560 g/day) for 10 days |
| 4th | 12 | 8 daily capsules (2 in the morning, 3 at noontime and 3 in the evening) (3.560 g/day) for 21 days |

During the studies, participants were allowed to use any concomitant conventional treatments including physical therapy, medications or epidural steroid injections, but experimental medications were disallowed. This was reported and recorded.

During the treatment intervals, self-assessment was recorded by each participant in individual patient diaries. For compliance control, participants brought with them at the end of treatment or sent later the used capsule container and the dated patient diary. Treatment compliance and any special event were recorded.

*Study Measures*

In the open-label study, before beginning treatment of the next cohort all participants in the previous cohort underwent comprehensive clinical and laboratory evaluations to ascertain safety. These included thorough medical history review, comprehensive physical examination and laboratory analyses of blood samples. Follow-up safety evaluations were conducted during the following intervals: 11–15 days, 22–25 days, 40–45 days and a telephone interview evaluation at 6–7 months after treatment initiation.

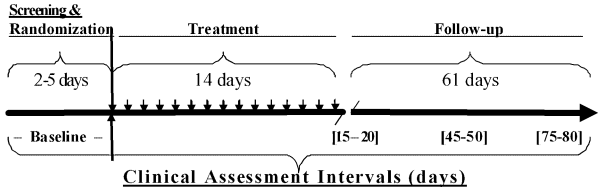


**Figure 1** A flowchart diagram of the trial time plan, including: screening, randomization, treatment and follow-up intervals.

In the RCT, during screening and after termination of treatment (15–20 day), participants underwent comprehensive clinical evaluation, which also included sensorimotor function tests, pain measures, health-related quality of life assessment, and laboratory analyses of blood samples. Follow-up measures (pain and health-related quality of life assessments) were obtained at 1 month (45–50 day) and 2 months (75–80 day) after treatment termination (see flowchart in Figure 1).

Safety evaluation was performed by analyses of clinical examinations and laboratory blood tests, and by evaluation of the participant diaries. Tolerability was assessed based on the number of participants who failed to complete the study of their free will or as a result of adverse effects, and on the time to withdrawal. Participants who prematurely discontinued remained under follow-up for the duration of the study.

Sensorimotor functions were determined according to standard measures of motor strength and sensation as detailed in the revised version of the International Standards for Neurological and Functional Classification of spinal cord injury, which grades motor score from 0 (total paralysis) to 5 (full muscle strength) and sensation from 0–2 ("0" meaning absent sensation and "2"-normal sensation). Muscle strength testing was performed against gravity and the examiner's manual strength, comparing both sides of the patient's lower extremities. The muscle groups tested were the iliopsoas (hip flexors), quadriceps (knee extensors), tibialis anterior (ankle dorsiflexors), extensor hallucis longus (long toe extensors), and gastrocnemius (ankle plantiflexors). Any muscle tested which was deemed less the 5/5 motor strength was considered abnormal. Additionally, deep tendon reflexes of the lower extremities were tested at the patellar tendon (testing for L2–3-4 root dysfunction) and Achilles tendon (testing for S1 nerve root dysfunction). As deep tendon reflexes reflect the motor function of a nerve root, any loss of a deep tendon reflex was considered as a sign (albeit subtle one) of motor dysfunction and was thus grouped together as "force/reflex."

Sensation was tested in the dermatomes of the lower extremities using the conventional dermatome chart. Light touch and pinprick sensation were tested to assess any sensory loss and graded from 0–2 as mentioned above. Any dermatome graded less than "2" constituted abnormal sensation.

Pain was evaluated using the following conventional tests with lower scores indicating less pain: 1) the visual analog scale for back and leg pain, graded from 0 (no pain) to 10 (10 points); 2) the McGill Pain Questionnaire composed of 15 questions graded from 0–3 each (45 points) [51]; and 3) the Oswestry Disability Index composed of 10 descriptors graded from 0–5 each (50 points) [52]. Measurements of general health-related quality of life status was assessed by the 36-item short form (SF-36) questionnaire, designed to quantitatively assess "physical health" and "mental health" dimensions by overlapping sets of questions whereby a score between 0 and 100 can be calculated, with a higher score indicating a better state of health [52–55].

Computerized tomography was performed to diagnose the disc pathology [56]. Hematology and clinical chemistry tests were performed on blood samples obtained before beginning and within 5 days after treatment termination, to ascertain normal function of the cardiovascular, hepatic, renal, immune, and metabolic systems.

*Data Handling and Statistical Analysis*

All records and data were identified only by participants' code number. All "source data" documents are stored in individual files and kept at the respective clinical center in the principal investigators' departments and copies are kept with the study sponsor.

The planned RCT protocol was based on past experience using the visual analog scale and the SF-36 health-related quality of life test scores and assuming a normally distributed population. Scores of these two tests can be straight forwardly calculated as percent changes as they are rated on a 10 and 100 point scale, respectively. It was estimated that a minimum sample size of 30 patients per group will be required to enter this two treatment parallel-design study with a probability of 80% that the study will detect a treatment difference at a two-sided 5% significance level, if the true clinically important difference between the treatments is 20%. This was based on the assumption that the standard deviation of the response variable is 27.

The randomization code was opened after the patients ended the last follow-up interval. The results were tabulated and presented by descriptive statistics including mean, standard deviation, and range (minimum and maximum) values. In performing statistical analyses, data from participants who discontinued treatment prematurely (did not finish the full, 14-day treatment course), were also included. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS vs 15.0, SPSS Inc., Chicago, IL). Differences in baseline characteristics between the placebo and agmatine sulfate-treated groups were analyzed by chi-square tests for categorical data, Fisher's exact test or Pearson chi-square test. For continuous data analyses, we used repeated measures analysis of variance (ANOVA) and 2-tailed paired *t*-test. To

**Table 2** Patient demographic characteristics, clinical status and adverse effects in the open-label study

| | Cohort | | | |
|---|---|---|---|---|
| Category | 1st | 2nd | 3rd | 4th |
| Number of participants (n): | 5 | 5 | 12 | 12 |
| Males | 3 | 1 | 7 | 8 |
| Females | 2 | 4 | 5 | 4 |
| Age (years) | | | | |
| Mean | 54.2 | 52.2 | 52.3 | 52.6 |
| Range | 31–63 | 40–59 | 28–70 | 36–64 |
| Participants with skeletal pathologies | | | | |
| Disc herniation | 3 | 1 | 7 | 7 |
| Disc degeneration | 1 | | 1 | |
| Spinal stenosis | 1 | 1 | | |
| Herniation + degeneration | | 1 | 1 | 1 |
| Herniation + stenosis | | 1 | 3 | |
| Herniation + degeneration + stenosis | | 1 | | 3 |
| Mean symptom duration (weeks) | 3.8 | 14 | 19.3 | 50.7 |
| Concomitant treatment (no. of participants) | | | | |
| Medication (Nonsteroidal anti-inflammatory drugs) | 3 | 1 | | |
| Physiotherapy | 2 | | | 1 |
| Adverse effects (no. of participants) (Nausea and diarrhea) | | | 1 | 2 |
| Discontinuations—due to adverse effects | | | | 1 |
| Free will discontinuations | | | | 1 |

assess symptoms improvement, data were normalized by plotting changes as the percent of pretreatment or baseline values. Normalized data served for group comparisons and differences were analyzed by 2- and 1-tailed paired *t*-test and by repeated measures ANOVA for multiple time points. Correlations between changes in study measures were performed by Pearson correlation test. Differences were considered significant at $P \leq 0.05$.

## Results

### *Safety and Tolerability*

The population descriptors of the open-label study are summarized in Table 2. Participants in this study were 34 men and women, 28–70 years of age diagnosed with various lumbosacral degenerative pathologies associated with radiculopathy lasting for various time intervals.

Agmatine sulfate was found to be safe by all measures used. Clinical examinations and laboratory analyses of blood samples revealed no abnormality in any parameter studied in all participants of the trial. During the treatment interval, only three participants reported mild-to-moderate adverse effects (Table 2). One participant of the 3rd cohort (3.560 g/day, for 10 days) and two of the 4th cohort (3.560 g/day, for 21 days) reported having discomfort as a result of mild-to-moderate diarrhea and nausea during treatment that began at 2–3 days and disappeared upon cessation of treatment. The latter two belonging to the 4th cohort discontinued the study. One of them at 10 days after starting the treatment as a result of the indicated adverse effect and the other discontinued after 7 days for personal reasons not related to the reported adverse effects. Both participants who discontinued remained under follow-up for the study duration. None of the above three participants had any other abnormality. In sum, only 2 of the 34 participants failed to complete the study, one as a result of free will discontinuation and the other as a result of mild-to-moderate adverse effects (Table 2).

None of the participants reported any health-related abnormality at any of the follow-up periods. Four participants elected to undergo corrective surgery for their condition: two participants, one from the 3rd and the other from the 4th cohort within 2 weeks after treatment termination, and one of the 3rd cohort and one of the 4th, underwent surgery 2 and 3 months after treatment, respectively.

In this open-label study, only few of the participants chose to use conventional treatments (e.g., NSAIDs and physiotherapy) (Table 2) and these treatments had no apparent effects on the outcomes. Effects of gender or age could not be discerned because of small sample size.

## Efficacy of Agmatine Sulfate

### *Participant Characteristics*

The flowchart of recruitment to the RCT is illustrated in Figure 2. Forty-six patients diagnosed with herniated lumbar disc syndrome were recruited at Tel-Aviv Sourasky Medical Center and 53 at Assaf Harofeh Medical Center.

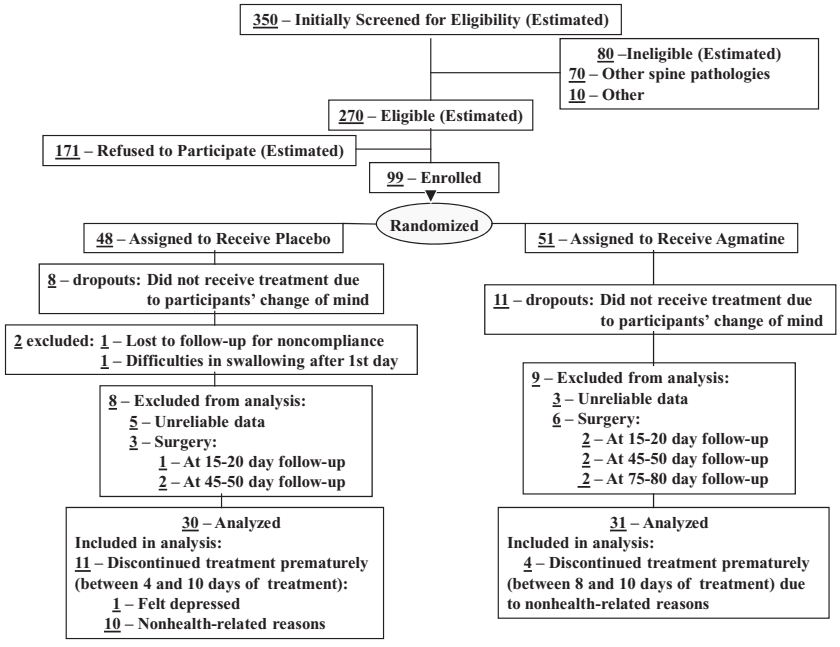


**Figure 2** A flowchart diagram of the number of patients recruited to the trial, including: screening, enrolment, randomization, follow-up, and analysis.

They were randomly assigned into the placebo (n = 48) and agmatine (n = 51) groups, but eight participants in the placebo and 11 in the agmatine group changed their mind before receiving treatment and dropped off the study (Figure 2). In the placebo-treated group, one participant decided to discontinue treatment after the first day of treatment and another one was lost to follow-up right after treatment before data recording. Additionally, eight participants in the placebo and nine in the agmatine group were excluded from analysis either as a result of unreliable data entry (five in the placebo and three in the agmatine group) or because they underwent surgery during the follow up period (three in the placebo and six in the agmatine group) (Figure 2). In total, 38 participants were excluded from analysis because they either dropped off prior to any data collection or because of unreliable data collection.

Only four participants in the agmatine as compared with 12 in the placebo group prematurely discontinued their treatment (Figure 2) and most of them—three in the agmatine and 11 in the placebo group—received treatment for at least 10 days of the 14-day course. One participant in the agmatine group continued treatment for just 8 days and one in the placebo group stopped taking treatment after only 4 days. These participants, however, were included in the data analysis (Figure 2). Treatment effects were thus, assessed based on "as-treated" data analyses with adjustments for missing and unreliable data and for the confounding effects of surgery. Analysis was performed on 30 participants in the placebo and 31 in the agmatine arm.

*Baseline Measures*

No significant differences in baseline demographic parameters, pain measurements and health-related quality of life were observed between the placebo and agmatine groups (Table 3). The level of the pathological discs did not differ significantly between the groups (Table 3) and neither did the overall severity of disc pathology (results not shown) as assessed by CT scans [56]. Patients found it difficult to clearly distinguish between lower back and leg pain; the majority described the pain as radiating from the back into regions of the leg (Table 3). For this reasons, the pain scores recorded in the present study refer to both back and leg pain.

The baseline sensorimotor neurological deficits, however, were more severe in the agmatine as compared with the placebo-treated group (Table 3).

No adverse effects were noted during the course of the trial. Throughout the trial, only two health-related discontinuations were noted and they occurred in the placebo-treated group. One participant felt depressed and the other had difficulties in swallowing. Safety of the agmatine regimen under study was studied as a secondary outcome. None of the participants showed any agmatine treatment-related abnormality as assessed by clinical examinations and laboratory analyses.

*Effects of Treatment*

Table 4 shows the changes in primary outcomes—pain severity and general health status—as percent of baseline values. Symptoms improved with time in both placebo and agmatine-treated groups, but improvements were more pronounced in the agmatine-treated group. Importantly, statistically significant enhanced improvements in the agmatine-treated group as compared with placebo were noted at the follow-up interval

**Table 3** RCT patient baseline demographic characteristics, clinical findings, general health status, and symptoms severity

| | Group | |
|---|---|---|
| Category | Placebo (n = 30) | Agmatine (n = 31) |
| Age (years)* | 44.8 ± 13.8 | 44.1 ± 12.7 |
| Range | 22–75 | 25–73 |
| Gender* | | |
| Female | 14 (46.7%) | 13 (41.9%) |
| Male | 16 (53.3%) | 18 (58.1%) |
| BMI*† | 25.4 ± 3.5 | 27.2 ± 5.6 |
| Current smoking* | 7 (25.9%) | 6 (20.7%) |
| Symptom duration (weeks)* | 7.9 ± 4.5 | 11.7 ± 15.4 |
| Range | 1–16 | 1–48 |
| Herniation level* | | |
| L3–4 | 2 (6.7%) | 3 (9.7%) |
| L4–5 | 13 (43.3%) | 10 (32.3%) |
| L5–S1 | 14 (46.7%) | 11 (35.5%) |
| L3–4 + L5–S1 | | 2 (6.4%) |
| L4–5 + L5–S1 | 1 (3.3%) | 5 (16.1%) |
| Herniation type* | | |
| Protrusion | 2 (6.7%) | 1 (3.2%) |
| Extrusion | 27 (90.0%) | 23 (74.2%) |
| Protrusion + extrusion | 1 (3.3%) | 7 (22.6%) |
| Pain location* | | |
| Back pain only | 3 (10.0%) | 1 (3.2%) |
| Back + leg pain | 27 (90.0%) | 30 (96.8%) |
| Pain measures* | | |
| Visual analog scale | 6.5 ± 2.3 | 6.9 ± 2.1 |
| McGill Pain Questionnaire | 21.9 ± 9.4 | 22.6 ± 9.8 |
| Oswestry Disability Index | 28.2 ± 8.2 | 25.7 ± 11.9 |
| Quality of life assessment–SF-36 score* | | |
| Total score | 33.8 ± 15.5 | 37.3 ± 21.4 |
| Physical health score | 34.7 ± 13.3 | 35.0 ± 19.5 |
| Mental health score | 40.2 ± 18.9 | 43.0 ± 22.9 |
| Neurological deficits‡ | | |
| Sensory–unilateral decrease | 7 (23.3%) | 20 (64.5%) |
| Motor (force/reflex)–unilateral weakness | 16 (53.3%) | 25 (80.6%) |

Results are the mean ± SD values. In parentheses—the numbers of participants in any categorical parameter are expressed as the percent of sample size.

* Nonsignificant between-group differences at $P \geq 0.17$.

† BMI values are calculated as kg/m$^2$ (weight in kg divided by the square of height in meters).

‡ Significant between-group differences at $P \leq 0.05$.

BMI = body mass index.

immediately after treatment termination (15–20 days). When expressed as percent improvement over baseline values, the following differences were noted in pain measures (Table 4): visual analog scale—4.8% improvement in placebo as compared with 25.0% in the agmatine group ($P = 0.033$ by 2-tailed paired *t*-test) and McGill Pain Questionnaire—7.1% improvement in placebo as compared with 28.4% in the agmatine group ($P = 0.032$ by 2-tailed paired *t*-test). The range of differences in general health status as assessed by SF-36 was 16–24% improvement in placebo as compared with 65.5–76.2% in the agmatine group (total score, and physical dimension score, $P = 0.013$ and $P = 0.008$, respectively, by 2-tailed paired *t*-test, and $P \leq 0.05$ by repeated ANOVA; mental dimension score, $P = 0.027$ by 2-tailed paired *t*-test).

Overall, the observed improvements in pain measures are significantly correlated with general health status as assessed by SF-36 scores (negative *r*-values range = –0.28 to –0.54; *P* values range = 0.03–0.0001). This inverse relationship can be appreciated in Figure 3,

**Table 4** Changes in the RCT primary outcomes—pain severity and general health status—at the specified follow-up time intervals

| | Follow-up Interval (Percent of Baseline) | | |
|---|---|---|---|
| Measure (Baseline Scores) | 15–20 Day | 45–50 Day | 75–80 Day |
| Pain measurements† | | | |
| Visual analog scale | | | |
| Placebo (6.5 ± 2.3) | 95.2 ± 49.3 | 69.0 ± 47.3* | 64.6 ± 46.8* |
| Agmatine (6.9 ± 2.1) | 75.0 ± 33.4*,** | 59.7 ± 42.1* | 45.5 ± 43.1* |
| McGill Pain Questionnaire | | | |
| Placebo (21.9 ± 9.4) | 92.9 ± 43.3 | 56.9 ± 47.0* | 55.6 ± 48.0* |
| Agmatine (22.6 ± 9.8) | 71.6 ± 31.6*,** | 56.9 ± 40.4* | 49.5 ± 67.2* |
| Oswestry Disability Index | | | |
| Placebo (28.2 ± 8.2) | 78.6 ± 29.7* | 55.0 ± 37.2* | 51.5 ± 38.2* |
| Agmatine (25.7 ± 11.9) | 72.0 ± 26.5* | 61.9 ± 36.6* | 43.4 ± 38.4* |
| General health status‡ | | | |
| SF-36 total score | | | |
| Placebo (33.8 ± 15.5) | 124.0 ± 38.0* | 181.0 ± 95.7* | 195.4 ± 101.9* |
| Agmatine (37.3 ± 21.4) | 176.2 ± 105.2*,*** | 192.6 ± 120.1* | 227.2 ± 134.1* |
| SF-36 Physical Health Score | | | |
| Placebo (34.7 ± 13.3) | 116.4 ± 40.1* | 167.4 ± 81.8* | 176.0 ± 69.0* |
| Agmatine (35.0 ± 19.5) | 167.9 ± 95.2*,*** | 194.5 ± 118.9* | 223.4 ± 117.4*,** |
| SF-36 Mental Health Score | | | |
| Placebo (40.2 ± 18.9) | 124.0 ± 44.8* | 171.9 ± 116.6* | 173.0 ± 85.4* |
| Agmatine (43.0 ± 22.9) | 165.5 ± 90.0*,** | 174.4 ± 97.5* | 195.1 ± 106.5* |

Results are the mean ± SD values expressed as percent of baseline values (shown in parenthesis).
* Significant as compared with baseline values $P \leq 0.05$; ** Significant between-group differences at (2-tailed paired *t*-test, $P \leq 0.05$); *** Significant between-group differences (by 2-tailed paired *t*-test, $P \leq 0.05$ and by repeated ANOVA, $P \leq 0.05$).
† Lower score indicates less severe symptoms.
‡ Higher score indicates less severe symptoms.

which illustrates post-treatment improvements in visual analog scale and in SF-36 total score over time and the significant between-group differences at the 15–20 days follow-up interval.

Table 5 shows group differences in categorical variables—sensorimotor neurological deficits and the secondary outcome measures, treatments other than the agmatine or placebo, and corrective surgery—between the 14-day treatment interval and the full post-treatment follow-up period. Significantly more participants with unilateral sensory reduction ($P = 0.002$) and motor weakness ($P = 0.031$) began treatment in the agmatine group as compared with placebo. Importantly however, while the group difference in the sensory deficits persisted following the treatment, the number of participants with motor weakness who took agmatine decreased, but they remained unchanged in the placebo group.

No group differences in secondary outcomes were observed between the 14-day treatment interval and the full post-treatment follow-up period. Thus, the number of participants on pain medications: NSAIDs, opioid analgesics, or epidural steroid injection, those who used physical therapy (including: physiotherapy and chiropractic therapy), or those who underwent standard diskectomy for corrective surgery, did not differ significantly between the groups.

## Discussion

Results of the present studies clearly indicate that dietary agmatine sulfate can be considered safe for human use when taken under the specified dose-range and duration. The RCT study demonstrates that during the period immediately after taking agmatine sulfate people suffering from lumbar disc-associated radiculopathy undergo significant improvement in their symptoms and in general health-related quality of life as compared with those taking placebo. Importantly, no significant side-effects were observed with dietary agmatine sulfate.

### *Side Effects*

Three participants reported discomfort as a result of mild-to-moderate diarrhea and nausea that appeared 2–3 days after taking the high dose (3.560 g/day) of agmatine sulfate. These symptoms disappeared within 1–2 days after treatment cessation. Only one participant, however,

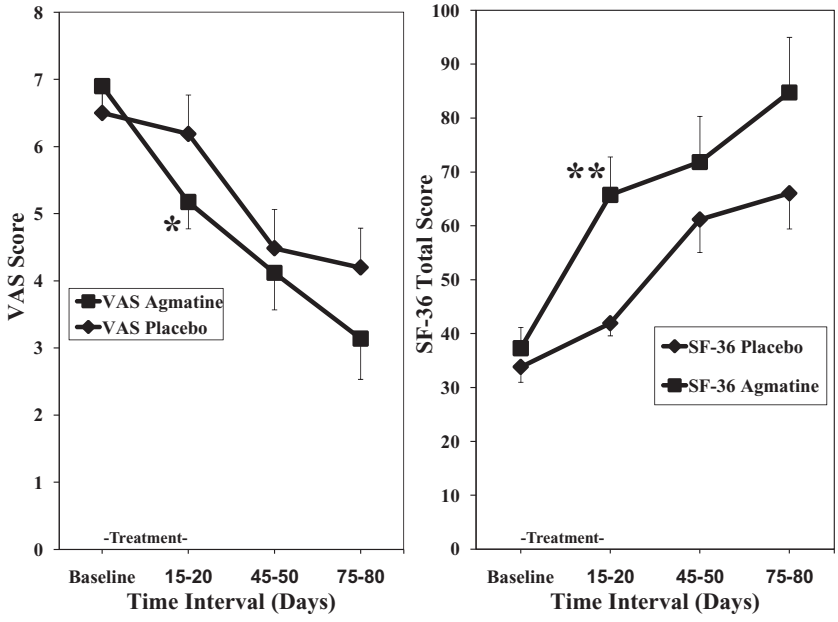


**Figure 3** Changes in visual analog scale (VAS score, left panel) and in SF-36 total score (right panel) at the specified time intervals after initiation of placebo and agmatine sulfate treatments. Results are the mean ± SEM (vertical lines) values. *Significant differences between the placebo- and agmatine sulfate-treated groups by 2-tailed paired *t*-test ($P \leq 0.033$). **Significant differences between groups by 2-tailed paired *t*-test ($P \leq 0.01$) and by repeated measures ANOVA ($P \leq 0.018$).

chose to discontinue for that reason. None of the affected participants required any treatment related to the side-effects. These mild side-effects were initially predicted for two reasons: One, sulfate salts (e.g., magnesium sulfate [Epsom salt] and sodium sulfate [Glauber's salt]) are long known to stimulate peristaltic action and are used therapeutically as purgative or cathartic agents; and two, guanidine group-containing dietary ingredients, arginine and creatine, are also known to cause mild diarrhea and nausea at high doses. Additionally, these mild side effects were expected based on previous experience with a group of nine people, who elected, on their own cognizance, to take agmatine sulfate on a continuous basis for a year (beginning October–November 2005). Three individuals developed transient mild diarrhea and gas which began 1–3 days after treatment initiation and subsided within several days thereafter.

*Disease Characteristics and Relevance to the RCT Design*

The natural history of herniated lumbar disc causing nerve root compression is in general very favorable, with up to 70–80% of patients showing relief of pain symptoms within 6–12 weeks while in the rest, symptoms usually subside gradually and only a small portion still suffer symptoms after 1 year [3,4]. This is because most herniated lumbar disc or disc protrusions resolve spontaneously with time [57]. Recent studies further indicate that the general favorable history of the long-term symptom improvement with conservative treatment may be comparable to the outcome of corrective surgery [58–60]; however, this is controversial ([61] and may not persist over extended periods of years [62]). Conservative treatment consists of light exercise, physiotherapy, and/or NSAIDs medication, but opioids analgesics are often prescribed. Still, the associated pain is often not responsive to those treatments and remains a major reason for patient complaints and thus, an unmet clinical and health-related issue [6].

The study objective was to test the hypothesis that there was no difference between placebo and agmatine sulfate treatment with respect to pain and disability in patients with lumbar disc-associated radiculopathy. This is not a completely homogeneous syndrome with respect to the degree of pain and sensorimotor dysfunction, the clinical course and treatment response [63]. Additionally, the relationship between pain and herniated disc location (i.e., central, posterolateral, foraminal, or far lateral) and morphological features (i.e., protrusion, extrusion, or sequestration) is also uncertain [64]. The hypothesis is, nevertheless, justified when comparisons are made between sufficiently large groups with comparable baseline measures, as is the case of the present study.

Three disadvantageous factors are inherent in the present study design. A) The spontaneous recovery peculiar to

**Table 5** Differences between the placebo and agmatine groups in the number of participants with sensorimotor neurological deficits or those who received other treatments or undergone corrective surgery—between the 14-day treatment interval and the full post-treatment follow-up period

| | Number of Participants | |
|---|---|---|
| Category | During Treatment | Post-Treatment |
| Neurological deficits | | |
| Sensory–unilateral decrease | | |
| Placebo | 7 (23.3%) | 8 (26.7%) |
| Agmatine | 20 (64.5%)** | 17 (54.8%)** |
| Motor (force/reflex)–unilateral weakness | | |
| Placebo | 16 (53.3%) | 16 (53.3%) |
| Agmatine | 25 (80.6%)** | 20 (64.5%) |
| Other treatments | | |
| Medications* | | |
| Nonsteroidal anti-inflammatory drugs | | |
| Placebo | 15 (50.0%) | 15 (50.0%) |
| Agmatine | 11 (35.5%) | 9 (29.0%) |
| Opioid analgesics | | |
| Placebo | 0 | 0 |
| Agmatine | 2 (6.5%) | 1 (3.2%) |
| Epidural steroid injection | | |
| Placebo | 1 (3.3%) | 1 (3.3%) |
| Agmatine | 0 | 1 (3.2%) |
| Physical therapy (including: physiotherapy, chiropractic therapy)* | | |
| Placebo | 13 (43.3%) | 14 (46.7%) |
| Agmatine | 7 (22.2%) | 8 (25.8%) |
| Surgery (standard diskectomy)* | | |
| Placebo | 0 | 2 (6.7%) |
| Agmatine | 0 | 4 (12.9%) |

Results in parentheses, are the numbers of participants expressed as percent of sample size.
* Nonsignificant between-group differences at $P \geq 0.11$.
** Significant between-group differences at $P \leq 0.05$.

symptomatic herniated lumbar discs by endogenous repair mechanisms (e.g., resorption, receding inflammation and reducing local edema), which occurs in the majority of patients within 3 months with conservative treatment [5]. This is probably the reason for symptoms improvement over time in both the placebo and agmatine sulfate-treated groups (but note also factor C below). B) During the study, participants were allowed any concomitant conservative treatment, including NSAIDs, opioid analgesics, and epidural steroid injection as pain reducing medications. C) The large placebo effect in sciatica and other degenerative neurological disorders may exceed 30%, thus effectively reducing experimental treatment effect, but underlies the absolute requirement for placebo control studies [65,66]. Yet in spite of these confounding factors, the demonstration of agmatine sulfate efficacy in exerting a significantly more pronounced relief of symptoms for the period lasting few days after treatment termination is exceptional.

A comment is in order about the participant withdrawal rate from the study. While eight participants assigned to the placebo and 11 to the agmatine group withdrew prior to receiving any treatment, 10 and 9 participants of the placebo and agmatine groups, respectively, were excluded after beginning treatment. This latter numbers constitute about 20% of the initial recruitment (48 in the placebo and 51 in the agmatine group) and may be associated with bias. A follow-up study with a larger number of participants will validate the present findings and resolve these issues.

### *Postulated Mechanisms of Action*

Ample preclinical evidence indicates that ingested agmatine sulfate can be absorbed and modulate multiple molecular targets in the body [67]. These include key neurotransmitter receptors, ionic channels, NO synthesis, cell signaling pathways, and AGE-product formation [30–43,45,49,50]. These molecular mechanisms underlie both neuroprotective and pain-reducing effects of agmatine sulfate [22–30,68–70]. They may also be the underlying mode of action for the observed beneficial effects of

agmatine in those with herniated lumbar disc-associated radiculopathy.

*Future Indications*

The improvement of symptoms was more pronounced in the agmatine sulfate-treated as compared with the placebo cohort, but differences achieved statistical significance only during the follow-up interval immediately after treatment cessation (15–20 day follow-up interval) and dissipated at later follow up intervals. This suggests that the treatment accelerated the recovery process (see Figure 3). Treatment duration longer than the 14 day regimen currently studied, might improve the outcome further. Clearly this would be the goal of a follow-up study focusing particularly on the effects of agmatine sulfate on the speed of rehabilitation and long-term disability.

**Acknowledgments**

We thank the patients for participating in the study. We acknowledge the help of Ilana Gelernter, MA, of the Statistical Laboratory, School of Mathematics, Tel Aviv University, in the statistical analysis of the data. The study was supported in part by Trimaco Medical Division Ltd, Rehovot, Israel, and by G & V Gilad, Ltd, Tel Aviv, Israel.

**References**

1 Weber H. Spine update: The natural history of disc herniation and the influence of intervention. Spine 1994;19:2234–8.

2 Frymoyer JW. Back pain and sciatica. N Engl J Med 1988;318:291–300.

3 Weber H. Lumbar disc herniation. A controlled prospective study with ten years of observation. Spine 1983;8:131–40.

4 Hofstee DJ, Gijtenbeek JMM, Hoogland PH, et al. Westeinde sciatica trial: Randomized controlled study of bed rest and physiotherapy for acute sciatica. J Neurosurg (Spine 1) 2002;96:45–9.

5 Vroomen PC, de Krom MC, Knottnerus JA. Predicting the outcome of sciatica at short-term follow-up. Br J Gen Pract 2002;52:119–23.

6 Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. Curr Pain Headache Rep 2009;13:185–90.

7 Rydevik B, Brown MD, Lundborg G. Pathoanatomy and Pathophysiology of nerve root compression. Spine 1984;9:7–15.

8 Hoke A. Neuroprotection in the peripheral nervous system. Rationale for more effective therapies. Arch Neurol 2006;63:1681–5.

9 Cajal SRY. Degeneration and Regeneration of the Nervous System. Translated Ed. May RM. New York: Oxford University Press; 1928.

10 Kobayashi S, Uchida K, Yayama T, et al. Motor neuron involvement in experimental lumbar nerve root compression. A light and electron microscopy study. Spine 2007;32:627–34.

11 Sekiguchi Y, Kikuchi S, Meyers RR, Campana WM. Erythropoietin inhibits spinal neuronal apoptosis and pain following nerve root crush. Spine 2003;28:2577–84.

12 Tabor CW, Tabor H. Polyamines. Annu Rev Biochem 1984;53:749–90.

13 Bauza T, Blaise A, Daumas F, Cabanis JC. Determination of biogenic amines and their precursor amino acids in wines of the Vallee du Rhone by high-performance liquid chromatography with precolumn derivatization and fluorimetric detection. J Chromat 1995;707:373–9.

14 Izquierdopulido M, Hernandezjover T, Marinefont A, Vidalcarou MC. Biogenic amines in European bears. J Agric Food Chem 1996;44:3159–63.

15 Morris B. Bio-functional legumes with nutraceutical, pharmaceutical, and industrial uses. Economic Botany 2003;57:254–61.

16 Gloria MB, Tavares-Neto J, Labanca RA, Caevalho MS. Influence of cultivar and germination on bioactive amines in soybeans. J Agric Food Chem 2005;53:7480–5.

17 Kawabata T, Obshima H, Ino M. Occurrence of methylguanidine and agmatine in foods. IARC Sci Publ 1978;19:414–23.

18 Ruiz-Capillas C, Moral A. Formation of biogenic amines in bulk-stored chilled hake (Merluccius merluccius L.) packed under atmospheres. J Food Prot 2001;64:1045–50.

19 Swanson KS, Grieshop CM, Flickinger EA, et al. Fructooligosaccharides and Lactobacillus acidophilus modify bowel function and protein catabolites excreted by healthy humans. J Nutr 2002;132:3042–50.

20 Molderings GJ, Heinen A, Menzel S, et al. Gastrointestinal uptake of agmatine: Distribution in tissues and organs and pathophysiologic relevance. Ann NY Acad Sci 2003;1009:44–51.

21 Piletz JE, May PJ, Wang G, Zhu H. Agmatine crosses the blood-brain barrier. Ann NY Acad Sci 2003;1009:64–74.

22 Raasch W, Schafer U, Chun J, Dominiak P. Biological significance of agmatine, and endogenous ligand at imidazoline binding sites. J Pharmacol 2001;133:755–80.

23 Gilad GM, Salame K, Rabey JM, Gilad VH. Agmatine treatment is neuroprotective in rodent brain injury models. Life Sci 1995;58:PL41–6.

24 Gilad GM, Gilad VH. Accelerated functional recovery and neuroprotection by agmatine after spinal cord ischemia in rats. Neurosci Lett 2000;296:97–100.

25 Fairbanks CA, Schreiber KL, Brewer KL, et al. Agmatine reverses pain induced by inflammation, neuropathy, and spinal cord injury. Proc Natl Acad Sci USA 2000;97:10584–9.

26 Kim JH, Yenari MA, Giffard RG, et al. Agmatine reduces infarct area in a mouse model of transient focal ischemia and protects cultured neurons from ischemia-like injury. Exp Neurol 2004;189:122–30.

27 LeBlanc MH, Feng YZ, Piletz JE. Agmatine suppresses nitric oxide production and attenuates hypoxic-ischemic brain injury in neonatal rats. Soc Neurosci Online Program 2002;Abstract No: 391.11.

28 Bence AK, Worthen DR, Stables JP, Crooks PA. An in vivo evaluation of the antiseizure activity and acute neurotoxicity of agmatine. Pharmacol Biochem Behav 2003;74:771–5.

29 Berenholz L, Segal S, Gilad VH, et al. Agmatine treatment and vein graft reconstruction enhance recovery after experimental facial nerve injury. J Peripher Nerv Syst 2005;10:319–28.

30 Feng Y, Piletz JE, LeBlanc MH. Agmatine suppresses nitric oxide production and attenuates hypoxic-ischemic brain injury in neonatal rats. Pediatr Res 2002;52:606–11.

31 Kotil K, Kuscuoglu U, Kirali M, et al. Investigation of the dose-dependent neuroprotective effects of agmatine in experimental spinal cord injury: A prospective randomized and placebo-control trial. J Neurosurg Spine 2006;4:392–9.

32 Zomkowski AD, Hammes L, Lin J, et al. Agmatine produces antidepressant-like effects in two models of depression in mice. Neuroreport 2002;13:387–91.

33 Lavinsky D, Arteni NS, Netto CA. Agmatine induces anxiolysis in the elevated plus maze task in adult rat. Behv Brain Res 2003;14:19–24.

34 Gilad GM, Gilad VH, Rabey JM. Arginine and ornithine decarboxylation in rodent brain; coincidental changes during development and after ischemia. Neurosci Lett 1996;216:33–6.

35 Loring RH. Agmatine acts as an antagonist of neuronal nicotinic receptors. Br J Pharmacol 1990;99:207–11.

36 Pinthong D, Hussain JF, Kendall DA, Wilson VG. Comparison of the interaction of agmatine and crude methanolic extracts of bovine lung and brain with alpha(2)-adrenergic binding sites. Br J Pharmacol 1995;115:689–95.

37 Reis DJ, Regunathan S. Agmatine: A novel neurotransmitter? Adv Pharmacol 1998;42:645–9.

38 Yang XC, Reis DJ. Agmatine selectively blocks the N-methyl-D-aspartate subclass of glutamate receptor channels in rat hippocampal neurons. J Pharmacol Exp Therap 1999;288:544–9.

39 Shepherd RM, Hashmi MN, Kane C, Squires PE, Dunne MJ. Elevation of cytosolic calcium by imidazolines in mouse islets of Langerhans: Implications for stimulus-response coupling of insulin release. Br J Pharmacol 1996;119:911–16.

40 Xie-Chuan W, Xiao-Dan G, Jian-Quan Z, Jin L. Agmatine blocked voltage-gated calcium channel in cultured rat hippocampal neurons. Acta Pharmacol Sin 2003;24:746–50.

41 Komori Y, Guillermo CW, Fukuto JM. Inhibition of purified nitric oxide synthase from rat cerebellum and macrophage by l-arginine analogs. Arch Biochem Biophys 1994;315:213–18.

42 Auguet M, Viossat I, Marin JG, Chabrier PE. Selective inhibition of inducible nitric oxide synthase by agmatine. Jpn J Pharmacol 1995;69:285–7.

43 Galea E, Regunathan S, Eliopoulus V, Feinstein DL, Reis DJ. Inhibition of mammalian nitric oxide synthases by agmatine, an endogenous polyamine formed by decarboxylation of arginine. Biochem J 1996;316:247–9.

44 Gilad GM, Wollman Y, Iaina A, et al. Metabolism of agmatine into urea but not into nitric oxide in rat brain. NeuroReport 1996;7:1730–2.

45 Murayama T, Tsai S-C, Adamik R, Moss J, Vaughan M. Effects of temperature on ADP-ribosylation factor stimulation of cholera toxin activity. Biochem 1993;32:561–7.

46 Yang MZ, Mun CH, Choi YJ, et al. Agmatine inhibits matrix metalloproteinase-9 via endothelial nitric oxide synthase in cerebral endothelial cells. Neurol Res 2007;29:749–54.

47 Kawasaki Y, Xu ZZ, Wang X, et al. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. Nat Med 2008;14(3):331–6.

48 Dang AB, Tay BK, Kim HT, et al. Inhibition of MMP2/MMp9 after spinal cord trauma reduces apoptosis. Spine 2008;33:E576–9.

49 Vlassara H, Bocala R, Striker L. Pathogenic effects of advanced glycosylation: Biochemical, biological, and clinical implications for diabetes and aging. Lab Invest 1994;70:138–51.

50 Marx M, Trittenwein G, Aufricht C, Hoeger H, Lubec B. Agmatine and spermidine reduce collagen accumulation in kidneys of diabetic db/db mice. Nephron 1995;69:155–8.

51 Prieto EJ, Hopson L, Bradley LA, et al. The language of low back pain: Factor structure of the McGill pain questionnaire. Pain 1980;8:11–19.

52 Bombardier C. Outcome assessments in the evaluation of treatment of spinal disorders: Summary and general recommendations. Spine 2000;25:3100–3.

53 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

54 Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang H, Lazarus JM. Quality-of-life evaluation using Short Form 36: Comparison in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 2000;35:293–300.

55 Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. J Am Soc Nephrol 2001;12:2797–806.

56 Sachs BL, Vanharanta H, Spivey MA, et al. Dallas discogram description: A new classification of CT/discography in low back disorders. Spine 1987;12:287–94.

57 Gibson JN, Grant IC, Waddell G. The Cochran review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. Spine 1999;24:1820–32.

58 Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation. The Spine Patient Outcomes Research Trial (SPORT): Observational Cohort. JAMA 2006;296:2451–9.

59 Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation. The Spine Patient Outcomes Research Trial (SPORT): A randomized trial. JAMA 2006;296:2441–50.

60 Thomas KC, Fisher CG, Boyd M, et al. Outcome evaluation of surgical and nonsurgical management of lumbar disc protrusion causing radiculopathy. Spine 2007;32:1414–22.

61 Tubach F, Beaute J. Natural history and prognostic indicators of sciatica. J Clin Epidemiol 2004;57:174–9.

62 Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical versus nonoperative treatment for lumbar disc herniation: Four-year results for the spine patient outcomes research trial (SPORT). Spine 2008;33:2789–800.

63 McCormick PC. The Spine Patient Outcomes Research Trial results for lumbar disc herniation: A critical review. J Neurosurg Spine 2007;6:513–20.

64 Pearson AM, Blood EA, Frymoyer JW, et al. SPORT lumbar intervertebral disk herniation and back pain. Does treatment, location, or morphology matter? Spine 2008;33:428–35.

65 Koes BW, Bouter LM, van der Heijden GJ. Methodological quality of randomized clinical trials on treatment efficacy on low back pain. Spine 1995;20:228–35.

66 de la Fuente-Fernandez R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. Lancet Neurol 2002;1:85–91.

67 Haenisch B, von Kügelgen I, Bönisch H, et al. Regulatory mechanisms underlying agmatine homeostasis in humans. Am J Physiol Gastrointest Liver Physiol 2008;295:G1104–10.

68 Kolesnikov Y, Jain S, Pasternak GW. Modulation of opioid analgesia by agmatine. Eur J Pharmacol 1996;296:17–22.

69 Ji RR, Strichartz G. Cell signaling and the genesis of neuropathic pain. Sci STKE 2004.

70 Cernak I. Recent advances in neuroprotection for treating traumatic brain injury. Expert Opin Investig Drugs 2006;15:1371–81.