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Prospective Evaluation of the Efficacy of Spinal Decompression via the DRX9000 for Chronic Low Back Pain

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Abstract

Twenty patients presenting with low back pain averaging approximately 5 years in duration were prospectively enrolled in a 6-week course of 20 motorized spinal decompression treatments via the DRX9000™ (Axiom Worldwide, Tampa, Fla). Two patients withdrew for protocol violations. For the remaining 18 patients, the baseline median verbal pain intensity score on an 11-point scale (0 = no pain; 10 = worst possible pain) decreased from 7 (25th to 75th percentile = 5–7) to 0 (25th to 75th percentile = 0–1) at study conclusion at Week 6 ($P < .0001$). No device-related adverse events occurred. Overall, 16 of 18 patients reported clinically significant pain improvement after noninvasive spinal decompression.

Key Words: Chronic back pain, spinal decompression, verbal pain score

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Introduction

Chronic low back pain is an expensive benign condition in industrialized countries.[1] It is one of the most frequent reasons for visits to primary care physicians,[2] for time taken off from work due to sickness or short-term disability, and for hospital admission and surgery.[3,4] One-third to two-thirds of adults will suffer from low back pain at some time.[5,6] The prevalence of low back pain increases with age, and women are affected more often than men, with a peak in the sixth decade that results in substantial medical costs.[7,8] Low back pain is the most common and most expensive reason for work disability among US men and a frequent cause of early retirement.[9]

Mechanical causes of low back pain may be either injury to lumbosacral muscles and ligaments, facet or sacroiliac joint arthropathy, or discogenic disease due to degenerative changes. Discogenic pain most commonly affects the lower back, buttocks, and hips.[10] The American College of Physicians and the American Pain Society recommend avoiding routine imaging and other diagnostic tests in patients with nonspecific low back pain. Patients with chronic low back pain who do not improve with self-care should consider noninvasive treatments including acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation.[11] Valid, peer-reviewed, prospective, randomized, clinical trials in appropriate patients with adequate outcome assessments still are needed for many treatment options for chronic low back pain.[12–14]

Although data exist that traction widens the intervertebral space,[15] reduces disc protrusion[16] and intradiscal pressure,[17] and improves motor-evoked potentials[18] and leg mobility,[19] systematic reviews have concluded that traction probably is not effective in improving low back pain compared to placebo, sham, or other treatments.[20,21] Traction can be delivered manually by the therapist via the weight of the patient through a suspension device or by the patient pulling the bars at the head of the table while lying on a specifically designed table. These types of traction can be dif-

ficult to standardize, and the patient may not tolerate the pull force, which may trigger paravertebral muscle contraction and affect efficacy.

Several different spinal decompression therapy systems have been developed to overcome these drawbacks. These systems include the DRX9000™ (Axiom Worldwide, Tampa, Fla), the VAX-D (Vat-Tech, Inc., Palm Harbor, Fla), SpineMED® (CERT Health Sciences, LLC, Baltimore, Md), and the Accu-SPINA® System (North American Medical Corporation, Aventura, Fla). The designs of these systems are different, including how patients are positioned for treatment. No comparative studies have been performed, and manufacturers recommend a varying number of sessions along with a variety of adjunctive therapies. A systematic review of what published clinical data exist suggests that data are too limited to determine whether spinal decompression provides incremental benefit to individuals over other nonsurgical treatments.[22] The goal of this prospective, single cohort study was to assess the efficacy of a spinal decompression system (the DRX9000) for patients with chronic low back pain using a standardized protocol.

Methods

The primary outcome was the verbal rating scale pain intensity score on an 11-point scale (0 = no pain; 10 = worst possible pain).

Hypothesis. Our hypothesis was that patients with chronic low back pain who undergo spinal decompression with a standardized 6-week regimen consisting of 20 treatments with the spinal decompression system (5 sessions per week for 2 weeks, followed by 3 sessions per week for 2 weeks and then by 2 sessions per week for the final 2 weeks) would experience > 50% reduction in their verbal score of pain intensity.

Power analysis for sample size. Mean pain scores at time of enrollment were assumed to equal 6 (standard deviation [SD] 3) with potential reduction in pain of 50%. To obtain 80% power at an α· level of 0.05, sample size was estimated as 20 patients.

Secondary objectives were to assess 1) safety and adverse events of the spinal decompression system when it was used in the office by staff members, 2) effects of the treatment protocol on patient function as measured by the Oswestry Disability Index, and 3) overall patient satisfaction. Oswestry Disability Index scores range from 0 (no limitations or disability) to 50 (maximum severe disability).

The study enrolled patients at 3 outpatient clinics in Tampa, Fla; Beverly Hills, Calif; and Naples, Fla. The spinal decompression systems were installed after approval of the respective institutional review boards. No clinical site investigator or any staff members had previous experience with the system. Instruction was provided for the office staff and site investigators regarding study protocol, data collection, and adverse event monitoring and reporting.

Patients were eligible for inclusion if they were at least 18 years of age, could provide written informed consent, agreed to 6 weeks of treatment sessions, and presented with chronic, nonoperative low back pain lasting at least 12 weeks. Patient symptoms were evaluated by medical history review, physical examination, and magnetic resonance imaging (MRI) within the previous 6 months to support a diagnosis of musculoskeletal or mechanical pathology, herniated discs, bulging or protruding intervertebral discs, degenerative disc disease, unsuccessful back surgery more than 6 months earlier, posterior facet syndrome, or sciatica. No included patients were candidates for surgery on the basis of their history, examination, and radiologic studies.

Table 1
Spinal Decompression Treatment Protocol

Treatment Sessions
28-minute active treatment sessions for 20 sessions over 6 weeks
5 sessions per week in Weeks 1 and 2
3 sessions per week in Weeks 3 and 4
2 sessions per week in Weeks 5 and 6
Additional therapy after spinal decompression sessions
Cold therapy to lumbar paraspinal area for 15 minutes
Back exercise after Week 2 with improved verbal pain score

Exclusion criteria were back fusion or placement of stabilization instrumentation or artificial discs; pregnancy; neurologic motor deficits; spinal cord compression or fracture; metastatic cancer; tumor; hematoma; infection; spinal stenosis with neurologic deficits or nerve root entrapment; bowel, bladder, or sexual dysfunction; litigation for a health-related claim (in process or pending for workers' compensation or personal injury); hemiplegia or paraplegia; alcohol or drug abuse; abdominal aortic aneurysm; or a history of severe cardiovascular or metabolic disease. Limitations of the spinal decompression system also led to the exclusion of patients with extremes of height (< 147 cm or > 203 cm) and body weight (> 136 kg).

Treatment Protocol

The spinal decompression system apparatus has built-in air bladders, disc angle pull adjustments, and harnesses and can increase the distraction force more slowly in the latter part of the decompression. A split table design is used to reduce friction on the lumbar muscles. Each spinal decompression session began with the patient being fitted with an adjustable lower body and upper body harness to fit the individual (Figure 1). The patient then stepped onto a platform at the base of the spinal decompression unit and was lowered into the supine position. The harness was tightened and attached to the upper and lower ends of the table, with a pillow under the patient's knees to prevent extension of the lumbar spine. The patient was handed a safety control button to press that would immediately release all tension if necessary.

The protocol included 20 sessions of spinal decompression over a 6-week period (Table 1). Distraction force and angle were determined by the patient's weight and the location of disc pain. Initial distraction force was adjusted to patient tolerance, starting at 4.54 kg less than half their body weight. If a patient described the decompression pull as "strong or painful," this distraction force was decreased by 10%–25%. In subsequent treatment sessions, the distraction force was increased as toler-

Figure 1. **A volunteer illustrates how the spinal decompression harness is attached for a treatment session.**

ed to final levels of 4.54 kg–9.07 kg more than half their body weight.

Patients were instructed to continue to use analgesics prescribed by their physicians before enrollment. Increased pain could be treated with additional NSAIDs or cyclooxygenase-2 inhibitors. The patient's physician was responsible for adjusting any adjunct medications to ensure the comfort of patients throughout the study.

At the end of the study, patients were asked, "How satisfied were you with the spinal decompression treatment (0–10 scale; 0 = not satisfied, 10 = very satisfied)?"

Data Collection and Statistics

Patient data, including treatment parameters, pain, and Oswestry Disability Index scores, and any adverse events (with the investigator's assessment of relevance to study treatment) were collected at each treatment session and with a daily diary. The primary pain endpoint was assessed by a mixed effect model with time (visit) and as fixed effects and subject as random effect. Due to the small pilot sample size, only summary statistics (n, mean, SD, median, range) was produced at each time point to test the hypothesis of pain score reduction. Since pain data are nonparametric, the median and interquartile range is presented.

Results

A total of 27 patients were screened for inclusion in the study. Three patients declined to participate and 4 did not meet one of the inclusion/exclusion criteria. Twenty patients were thus enrolled, the first on 1/5/07 and the last on 3/16/07 such that data collection ended on 4/27/07. Two of these 20 patients dropped out. One patient withdrew during the second week of treatment when his pain was discovered to be pelvic rather than discogenic in origin. A second patient was excluded after the third week when she revealed involvement in an unrelated personal injury claim (this is a per protocol exclusion

Table 2
Characteristics of 18 Patients with Low Back Pain who Underwent Spinal Decompression Treatment

Variable	Value
Male sex, %	66.7
Age, y*	46.6 (15)
Height, cm*	175 (11)
Weight, kg*	102 (44)
Race, %	
White	15 (83.3%)
Hispanic	3 (16.7%)
Symptom duration, wk*	266 (209)
Employment status, %	
Employed	14 (77.8%)
Retired	3 (16.6%)
Other	1 (5.6%)

*Values are expressed as mean (standard deviation).

criterion). Thus, data for 18 patients with a mean low back pain duration of 266 weeks (SD 209, range 20–520, median 286) were analyzed (Table 2).

The 18 patients had tried numerous therapies, including chiropractic (16 patients); muscle stimulation (10 patients); cold therapy and massage therapy (9 patients each); exercise therapy (6 patients); heat therapy, physical therapy, and transcutaneous electrical nerve stimulation (5 patients each); and acupuncture, lumbar support brace, epidural injection, and miscellaneous treatments (3 patients each). Table 3 summarizes their low back pain diagnoses.

The median verbal numerical pain intensity score decreased from baseline 7 (range 4–10, interquartile range [25th to 75th percentile], 5–7) to median of 0 (range 0–7, interquartile range [25th to 75th percentile], 0–1) at Week 6 ($P < .0001$) (Figure 2).

At the conclusion of the 6 weeks, 16 of the 18 patients reported improvement in low back pain > 50% from baseline. No patient required an opioid analgesic during or after the treatment sessions.

The median baseline Oswestry Disability Index score of 26 (interquartile range [25th to 75th percentile], 19.50–29.50, range 7–34) declined to 14 (interquartile range [25th to 75th percentile] 8.50–18.50, range 0–26) ($P < .0001$) by Week 3 of treatment to a final median at Week 6 of 3 (interquartile range [25th to 75th percentile] 1–6.50, range 0–26) ($P < .0001$) (Figure 3).

The reported adverse events included one episode of neck pain, possibly related to the decompression session. The other adverse events were deemed by the patients' physicians to be unrelated to the treatments: head colds and sinus headaches in 2 patients each and sinus infection, shoulder pain, influenza, vertigo, and adrenal insufficiency in 1 patient each.

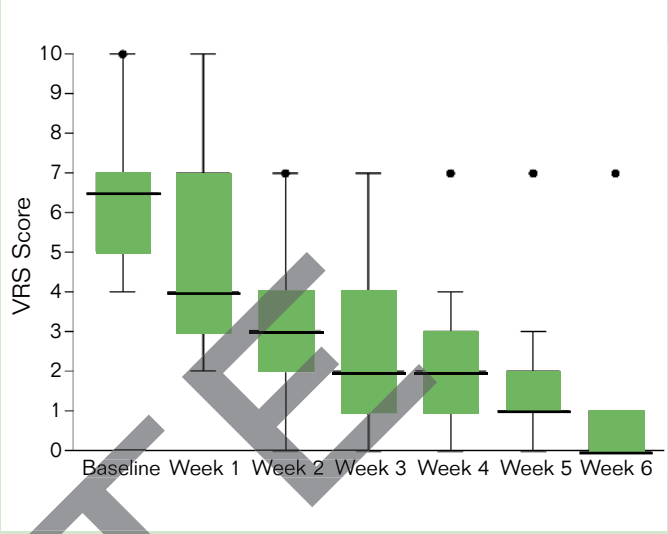

Figure 2. Box plot of weekly verbal rating scale pain scores of 18 patients with low back pain being treated with spinal decompression. Median interquartile range (25th to 75th percentile), minimum and maximum values, and outliers (indicated by dots) of the verbal pain score of patients completing the 20 treatment sessions with the spinal decompression system.

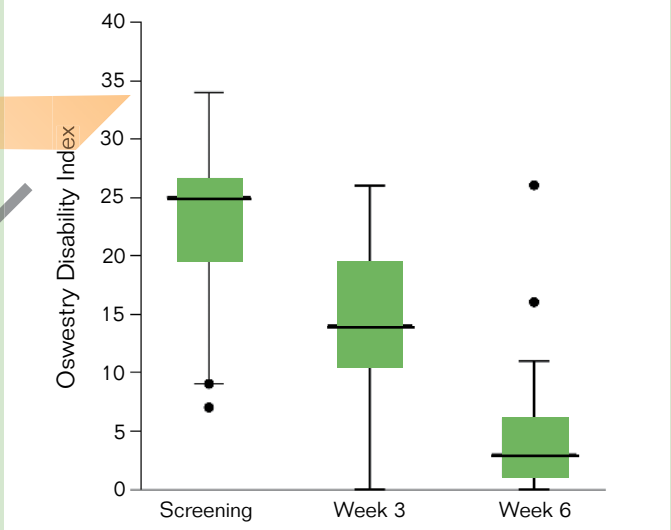

Figure 3. Mean Oswestry Disability Index scores, with median, interquartile range (25th to 75th percentile), minimum and maximum values, and outliers (indicated by dots) for 18 patients.

On a 0–10 scale, with 10 being the highest favorable rating, patients (data available for 14 of 18 patients) gave the spinal decompression treatments a mean rating of 7.61 (SD 1.9, range 4–10, 25th to 75th percentile 5–9) at the mid point of Week 3 and 8.1 (SD 3, range 0–10,

Table 3
Summary of Low Back Pain Diagnoses in 18 Patients

Variable	No. of Patients*
Diagnosis*	
Bulging or protruding disc	15
Degenerative disc	8
Herniated disc	6
Posterior facet syndrome	2
Failed back surgery	1
Location of Symptoms or Documented Pathology	
L1–L2	1
L2–L3	3
L3–L4	4
L4–L5	14
L5–S1	12

*Totals exceed 18 because some patients had multiple diagnoses and multiple levels of pathology.

25th to 75th percentile 7–10) after the final week (Week 6).

Sixteen of the 18 patients said that they would recommend this treatment protocol to others. The 2 patients who did not favor the treatment made the following statements: 1) "Did not work for me. Need more info on the type of back problems it works for and those it does not." 2) "No improvement from spinal decompression treatment."

Discussion

This is the first prospective evaluation of the efficacy of spinal decompression via the DRX9000 for the treatment of low back pain. Subjects were mostly Caucasian men in their 40s with discogenic lumbar back pain of several years in duration, with 78% being employed and 17% retired. The cohort had a median verbal numerical pain score of 7 on a 0–10 scale at time of initial presentation, which is consistent with pain scores obtained from patients with chronic low back pain in published studies.[23] Overall, 16 of 18 patients had clinically significant improvement as measured by a decline in chronic low back pain and improvement in the Oswestry Disability Index.

Investigators have reported that a minimum of 20 mm (out of 100 mm) difference on a self-reported visual analog scale is required to indicate a clinically important difference in chronic low back pain.[24] One could argue that the large benefit observed in this study might only be a temporary reversal in a chronic disease that has variable periods of low or high pain intensity. In fact, the natural history of low back pain has been hypothesized to be a reason for the proliferation of "unproved" treatments that may seem to be effective.[25] However, the long standing duration (often several years at the time of presentation) of pain in these patients as well as the large reduction in pain levels, along with the patients' qualitative positive comments, such as their satisfaction scores, support the argument that there is efficacy at the conclusion of 6 weeks with the spinal decompression system.

Discogenic pain is a major problem in lumbar degenerative disc disease and may be due to progressive annular breakdown and tearing, which stimulates pain fibers in the outer one-third of the annulus.[26] Experimental data exist to support the concept that spinal decompression reduces intradiscal pressure. This in turn may facilitate oxygen and nutrient uptake and improve disc metabolism and restoration.[27,28] However, oftentimes the anatomic cause of persistent low back pain remains unknown. Structural imaging and symptoms are poorly correlated.[29,30] Also, patients' baseline psychosocial variables may affect the development of chronic low back pain.[31] Job satisfaction, for example, remains a strong predictive factor for the identification of patients with acute low back pain who will develop chronic low back pain.[32] Certainly, a multidisciplinary approach can help patients with chronic discogenic low back pain by providing cognitive-behavioral therapy, patient education, NSAIDs, and physical therapy.

The results from our prospective clinical study are consistent with a retrospective medical record and outcomes analysis of 94 adults in 4 clinics (1 hospital-based and 3 free-standing) and suggested its clinical efficacy for in-office management.[33] The treatment protocol in that study included instruction on lumbar stretching exercises, myofascial release, or heat prior to spinal decompression treatment and the use of cold or muscle stimulation or both after the sessions. All clinical diagnoses were supported by MRI findings. In that study, the median pain duration before treatment was 260 weeks. Mean verbal rating pain scores equaled 6.05 at presentation and decreased significantly to 0.89 at the end of an 8-week treatment ($P < .0001$). Analgesic use also appeared to decrease, and activities of daily living improved. Follow-up (mean, 31 weeks) on 29 of the 94 patients reported mean pain improvement of 83%, mean verbal rating pain scores of 1.7, and satisfaction of 8.55 out of 10 (median, 9). No adverse events were identified in those patient records.

Such positive clinical outcomes warrant further investigation in a more rigorous prospective clinical study with an expanded patient population representing specific categories or lesions that result in chronic low back pain. In addition, the protocol of twenty 28-minute treatments should be explored to determine whether a dose-response curve exists. Less frequent treatment sessions would be easier to schedule, would be more appropriate for patients still working full time and trying to remain active, and could save the expense of additional sessions. A multivariate crossover trial design, for example, could help determine tension, angle of decompression, and frequency of treatment to minimize the number of treatments needed to achieve maximal efficacy and safety. As recommended by the manufacturer of the spinal decompression device, cold therapy was used as an adjunct treatment in this study. Other manufacturers have suggested different adjunct treatments in combination with decompression sessions, but no comparative trials are available.

The spinal decompression system used in the study was approved in May 2006 by the Division of General, Restorative, and Neurological

Devices in the US Department of Health and Human Services K060735. Its indications for use, per its 510(k) premarket notification of the manufacturer's intent to market the device, are as follows: "The DRX9000 True Non-Surgical Spinal Decompression System™ provides a primary treatment modality for the management of pain and disability for patients suffering with incapacitating low back pain and sciatica. It is designed to apply spinal decompressive forces to compressive and degenerative injuries of the spine. It has been found to provide relief of pain and symptoms associated with herniated discs, bulging or protruding intervertebral discs, degenerative disc disease, posterior facet syndrome, and sciatica."

Other spinal decompression systems available commercially are designed differently, such as position of patient (supine or prone), angle of pull (and whether it is adjustable), type of motor, use of feedback from tension sensors during distraction to attempt to minimize reflex muscle contraction, and measurement of delivered forces. These factors may lead to differing responses to therapy, so studies of one apparatus type should not be readily applied across all machines.

A systematic review by The Cochrane Library on the use of traction for low back pain with or without symptoms of sciatica documents little proof of efficacy.[34] Only 5 trials were considered of high quality. The types of traction reviewed included mechanical traction, manual traction (unspecified or segmental traction), autotraction, underwater traction, bed-rest traction, continuous traction, and intermittent traction. Data on this system of spinal decompression had not been published yet and thus were not available for inclusion in these analyses.

A limitation of our study was the end-point being the conclusion of the 6 weeks of treatment and not longer-term follow-up at one year, for example. Although it is encouraging to report that a 6-week course of in-office care will relieve chronic low back pain, we are unable to define recurrence rates from this study. Further studies will determine when repeat treatments may be needed and what might be a reasonable maintenance program after the 6-week treatment course. Another potential issue is that costs to the patient for the spinal decompression treatments were covered by the clinical research grant. Patients typically pay out-of-pocket for spinal decompression treatment although some payors do provide reimbursement. The free treatments provided as part of the clinical trial might have influenced patient interest in continuing and might even have influenced the efficacy they reported.

Conclusion

Of the patients completing the full 6-week course of spinal decompression, 16 of 18 reported improvement in pain. Patients also reported having better daily activity function as measured by the Oswestry Disability Index. No safety issues were identified. Future randomized, prospective, double-blind, long-term outcome trials will need to refine the treatment protocol and to allow a comparison of outcomes with other treatment options. ■

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Growth Hormone Replacement for Adults: An Overview

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Abstract

Physician and patient interest in growth hormone replacement therapy for adults is increasing. To provide a general and brief overview of the key issues related to human growth hormone, we arrived at group consensus on the topics that needed to be addressed, at least broadly, on growth hormone therapy for adults. We identified and cited key references for each topic, as well as included clinical applications based on one author's experience treating patients. We highlighted a few studies showing particular promise for growth hormone therapy. Studies, new and old, provide convincing evidence that growth hormone enhances health and quality of life. When acquired from a reliable, safe, approved pharmaceutical supplier and administered under proper clinical guidelines and at proper physiological dosages by a qualified physician, growth hormone may be a clinically safe and effective component of a broader preventative and maintenance therapy approach to a patient's health. Skepticism, however, remains over the benefits of growth hormone treatment. This article does not represent an exhaustive review of the literature; rather, it offers an environmental scan of hormone replacement therapy issues.

Key Words: Growth hormone replacement, deficiency, adults, safety, efficacy

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Growth Hormone and Maintaining Optimal Health

Research has demonstrated repeatedly that lifestyle changes can reduce the risk of diseases and health-compromising conditions. Not smoking, drinking alcohol moderately, lowering total and low-density lipoprotein (LDL) cholesterol levels, lowering high blood pressure, maintaining a healthy body weight, consuming a variety of healthy foods, engaging in regular physical activity, reducing stress, and ensuring sufficient sleep can help individuals optimize their health. Inadequate intake of several vitamins has also been linked to chronic diseases.[1]

Ample evidence additionally exists to show that maintaining optimal levels of the body's hormones is critical for vigor and vitality in the later years. Serum levels of many hormones decline with normal aging. Though the changes seen with aging are multifactorial, ample scientific data suggest that this normal hormonal decline is intimately involved. Specifically but not exclusively, growth hormone (GH) replacement therapy in aging adults has been shown to increase quality of life and prolong years of health.[2] Multi-year studies, well beyond the typical 6–12 month study protocols, have supported the positive benefits of growth hormone.[3,4] Research studies have documented that GH therapy can positively affect many of the changes seen with aging. Physiological supplementation has been shown to decrease weight, body fat mass, and fracture rate; increase lean body and muscle mass, exercise capacity, strength, and cognitive function; and improve bone density, poor sleep, sense of well being, and immune function.[5–11]

When combined with a comprehensive lifestyle and behavioral modification program, hormone optimization—the maintenance of hormone levels close to the levels of young adulthood when measures of health peak—including GH has the potential to maximize a broader preventative and maintenance therapy approach to health. Regardless of whether or not this statement will bear the scrutiny of a well designed, prospective study, ample evidence shows that this approach can help maximize an individual's years of good health. As stated, acceptance of this statement by the scientific community awaits further studies, but the following representative review of the literature suggests a basis for testing the validity of the hypothesis.

Growth Hormone Helps Chronic Disease

Growth hormone has been reported to assist patients better manage diseases including chronic bronchitis,[12] heart disease,[13–19] diabetes,[3,20–22] depression,[23,24] anxiety,[25–28] rheumatism,[29,30] and wasting syndromes.[31]

Cancer. Researchers and physicians have been concerned that GH could trigger undetected cancer cells to divide more rapidly and pro-

mote the growth of a tumor. While the question of whether GH increases the possibility of cancer is still unanswered, little in the literature supports this hypothesis. On the contrary, there are reasons to believe that GH replacement therapy given to cancer patients reduces cancer recurrence and mortality, as well as increases survival time.[32,33] In one study, long-term GH therapy (60 months) reduced the increased cancer risk and mortality of GH-deficient patients by half.[31]

Growth hormone therapy raises the levels of both insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). A high serum IGF-1 has been found to be associated with a lower risk of prostate cancer,[34-36] and a high serum IGFBP-3 has been associated with a reduced prostate cancer risk (~ 30%) and recurrence.[37]

History of Growth Hormone

In the 1920s, GH was purified from pig and cow pancreases for the treatment of type 1 diabetes. However, because of the significant variations in molecular structure between pig, cow, and human GH, pig and cow GH was not effective for humans.[38]

In 1958, Dr. Maurice Raben, a pioneering endocrinologist at the New England Medical Center in Boston, purified enough GH from human pituitary glands to successfully treat a GH-deficient boy. A few endocrinologists began to help parents of severely GH-deficient children make arrangements with local pathologists to collect human pituitary glands after removal at autopsy.[39]

Supplies of this "cadaver growth hormone" were limited and only the most severely deficient children were treated. From 1963 to 1985, about 7,700 children in the United States and 27,000 children worldwide were given GH extracted from human pituitary glands to treat severe GH deficiency. In the late 1960s, about 100 physicians trained in the new specialty of pediatric endocrinology around the world provided most of this care.[39]

It took thousands of cadaver brains to obtain the few drops of the hormone that could be injected into children's tissue. Most cadaver brains came from Africa and were shipped to commercial drug manufacturers where the hormone would be extracted from pituitary glands. Since heating the hormone would destroy it, the manufacturers sterilized the extract through a kind of pasteurization.[39]

However, by the 1980s, when three children who were taking GH extracts developed the same rare disease (Creutzfeldt-Jakob disease), the US Food and Drug Administration (FDA) ordered the distribution of the human GH drug stopped.[38,39] With the cadaver source lost, a GH drug had to be synthesized from scratch.

Scientific Mechanism of Recombinant Growth Hormone[39]

The anterior pituitary gland produces GH, which is a polypeptide consisting of 191 amino acids. Fashioning a molecule that size in a laboratory was a monumentally difficult task. In 1977, through new genetic engineering technology, Eli Lilly made a 191-amino acid GH that was identical—physically, chemically, and biologically—to the one made by the human pituitary.

Insulin-like growth factor-1. The pituitary gland releases GH in a pulsatile manner throughout the day. Having a very short half-life, GH only remains in the bloodstream for a few minutes. In the liver, GH stimulates the synthesis and release of growth factors (including IGF-1, also known as somatomedin C) and their binding proteins (including IGFBP-3).

The messenger that promotes most of the actions of GH, IGF-1 also has a longer half-life in the blood (being detectable for more than 12 hours) compared with GH whose half-life is less than 30 minutes. The largest release of GH occurs at night shortly after a person falls asleep. This makes accurate determination of peak levels difficult at best. Because of these reasons, IGF-1, rather than GH, is used as an indirect measure of GH secretion.

The clinical presentation of adult GH deficiency (AGHD) relates to findings, such as sarcopenia, increased body fat, osteoporosis, anxiety, fatigue, a diminished sense of well-being, and an unhealthy cholesterol profile.

Possibly due to the difficulty of accurately measuring GH levels, the laboratory diagnosis of AGHD has traditionally relied on a negative stimulation test (eg, insulin, arginine). However, there is some validity to diagnosing AGHD through documentation of low IGF-1 levels, since in a sense it is the "active hormone" and because it is the levels of IGF-1 present in the blood rather than the pituitary's potential ability to release GH (as reflected in a stimulation test) that is important. Similarly, one makes the diagnosis of diabetes through blood sugar and insulin levels, not through a pancreatic stimulation test.

Two main factors directly regulate the release of GH. One is GH-releasing hormone, which stimulates its release, and the other is somatostatin, which inhibits its release through a negative feedback loop that may involve GH itself. Exercise and dieting enhance GH release, while obesity and free fatty acids inhibit GH release.

Numerous studies support the relationship of healthy aging to IGF-1 levels, although it is a complex topic.[2]

Cellular rejuvenation. Until recently, one of the few ways we could limit damage to DNA was by taking antioxidant supplements, such as vitamins C and E, to bolster our own defenses and neutralize DNA-damaging intracellular free radicals. Growth hormone and IGF-1 act like carriers, bringing cells the raw materials needed for renovation and repair. Insulin-like growth factor-1 launches the delivery of the building blocks of the nucleic acids, DNA and RNA, right into the cell nucleus, where DNA resides. This allows for the efficient repair of damaged DNA and the stimulation of normal cell division.

Growth hormone also initiates the transport of amino acids, the building blocks of protein, and nucleic acids into the cytoplasm of the cell, the area outside the nucleus. This includes the cell membranes and intracellular organelles, such as the mitochondria. In this way, GH and IGF-1 do not just minimize the damage to the DNA and cellular structures; they also help repair the cell and the DNA. Growth hormone is probably the body's most important hormone of repair.

The supplementation of GH either by injections or by the use of GH secretagogues (amino acids, such as arginine, that may boost GH release) rejuvenates the cell's ability to repair itself and helps correct disturbances in homeostasis. Improved homeostasis means less disease and a healthier life span.

Diagnosing AGHD Syndrome

The AGHD syndrome is a documented deficiency disease. Most patients age 60 and older have total 24-hour human GH secretion rates indistinguishable from those of hypopituitary patients with organic pituitary gland lesions.[2] Growth hormone production by the pituitary declines by 1%–3% after the early 20s. By the time many adults reach 40 years, their GH levels have declined markedly regardless of the underlying etiology. If a mean IGF-1 of 300 ng/mL is normal for 20–30 year olds, this means that almost all men and women over the age of 40 have an IGF-1 deficit[40] and therefore might qualify for hormone replacement therapy. In a similar manner, when a man's testosterone levels decline to a significant degree, he is diagnosed with hypogonadism and treated with testosterone supplementation.

Symptoms of AGHD, such as increased body fat, decreased lean body mass, decreased bone density, impaired cardiac function, and other parameters,[3–5,41–43] may be sufficient for a clinical diagnosis of AGHD syndrome. As previously discussed, the current laboratory diagnosis of AGHD through stimulation testing, though noteworthy, may not accurately reflect the clinical condition.

Growth Hormone Replacement Therapy in Adults

Since the 1990 publication of an article by Rudman et al[44] suggesting that a short course of recombinant GH therapy could reverse aging-related changes in body composition in otherwise healthy men, GH use has increased rapidly in the United States and worldwide.[45]

The exact number of people who currently use GH is unknown. Some have reported that 20,000–30,000 people used GH in the United States as an anti-aging therapy in 2004, a more than 10-fold increase since the mid-1990s. Others claim that more than 100,000 people received GH without a prescription in 2002.[46]

Hundreds of studies since the seminal Rudman study have documented the value of GH replacement in otherwise healthy adults who have low IGF-1 levels.

Adult growth-hormone deficiency therapy. While a recently published meta-analysis by Liu et al[46] concluded that GH cannot be recommended as an anti-aging therapy, we excluded studies that evaluated GH as a treatment for a specific illness, including AGHD syndrome.

Hernberg-Stahl et al[47] tallied the number of doctor visits and hospital and sick-leave days from patients included in a pharmaco-epidemiological survey of hypopituitary adults with GH deficiency (for 6 months before GH treatment and 6–12 months after the start of treatment). Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. Quality of life (assessed using a disease-specific questionnaire, QoL-Assessment of Growth Hormone Deficiency in Adults) and satisfaction with physical activity during leisure time were assessed. For the total group (n = 304), visits to the doctor, number of days in the hospital, and amount of sick leave decreased significantly after 12 months of GH therapy. Patients needed less assistance with daily activities (significant only for men). Quality of life improved after 12 months of GH treatment, and both the amount of physical activity and satisfaction with level of physical activity improved after 12 months.[47]

Murray et al[48] administered a low-dose GH regimen to 67 adults with GH deficiency. Significant improvements in total cholesterol, LDL, triglycerides, and ratio of total cholesterol to high-density lipoprotein (HDL) were seen.[48]

Molitch et al[49] found that GH therapy offers benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures and that the risks of GH treatment are low.

Side effects. Additional studies have found that GH therapy in adults is tolerated with minimal or no side effects. Huang et al,[50] for example, cited the benefits of low-dose GH without mention of side effects.

In a single-center study of 118 adults with AGHD, Gotherstrom et al[3] examined the effects of 5 years of GH replacement on body composition, bone mass, and metabolic indices. The mean initial GH dose was 0.98 mg/day. The dose was gradually lowered, and after 5 years, the mean dose was reduced to 0.48 mg/day. The mean IGF-1 SD score increased from -1.73 at baseline to 1.66 at study end. A sustained increase in lean body mass and a decrease in body fat were observed. The GH treatment increased total body bone mineral content as well as lumbar (L2–L4) and femur neck bone mineral contents. Body mass density in lumbar spine (L2–L4) and femur neck were increased and normalized at study end. Total and LDL cholesterol decreased, and HDL cholesterol increased. At 5 years, serum concentrations of triglycerides and hemoglobin A (1c) were reduced compared with baseline values. The study concluded that 5 years of GH substitution in adults with GH deficiency is safe and well tolerated. The effects on body composition, bone mass, and metabolic indices were sustained. The effects on body composition and LDL cholesterol were seen after 1 year, whereas the effects on bone mass, triglycerides, and hemoglobin A (1c) were first observed after years of treatment.[3]

Gillberg et al[51] evaluated the safety and effects of a fixed low dose of GH, 0.17 mg/day for 3 months, on glucose metabolism, serum lipids, body composition, and cardiac function in 53 adults with GH deficiency. At 3 months, serum levels of IGF-1, IGFBP-3, and lipoprotein (a) and lean body mass increased. Total and LDL cholesterol levels and fat mass were reduced. There was a small but significant increase in the serum glucose value at 120 minutes after an oral glucose tolerance test (performed at 3 months). No other changes in glucose metabolism or cardiac function were noted. This fixed low-dose regimen resulted in improvements in body composition and lipid profile without causing serious side effects.[51] Other studies have noted that altered blood sugar levels return to normal after 6–12 months.

Table 1
Biomarkers on the Physiological Level of Overall Functioning

- Muscle mass/body fat ratio
- Weight
- Flexibility
- Bone density
- Forced vital capacity (measure of lung function)
- Aerobic capacity
- Tactile response time
- Forced expiratory volume
- Blood pressure and heart rate

Table 2
Key Biomarker Hormones

- Thyroid hormone (free T3, free T4, thyroid stimulating hormone)
- Testosterone (free and total)
- Dehydroepiandrosterone (DHEA)
- Insulin
- Estradiol
- Progesterone
- Cortisol
- Coenzyme Q10
- Antioxidant levels
- Prostate-specific antigen (PSA)
- C-reactive protein (test that measures the concentration of a protein in serum that indicates acute inflammation)
- Cholesterol profile

Ahmad et al[52] recommended the use of low-dose GH therapy after finding that it improves body composition and quality of life as early as 1 month after commencement, with beneficial effects continuing at 3 months, and that these changes occur in the absence of side effects.

No deaths or permanent life-threatening morbidities have been reported as a result of GH use by adults with GH deficiency who are otherwise healthy.[45]

Clinical Applications and Pathways[39,45,53]

Physical examinations and tests. In addition to the general physician workup, including a history and physical, blood cholesterol (LDL, HDL, and total), blood glucose, and blood pressure, some of the following tests should be conducted prior to instituting hormone replacement therapy at 1 month after therapy commencement and every 3 months thereafter once key biomarker hormone levels are stable.

Level 1. Overall body function. Biomarkers on the physiological level of overall functioning are listed in Table 1.

Level 2. Laboratory analysis. Biomarkers, including biochemical assays of key biomarker hormones, should be checked and optimized as part of a comprehensive health program; these hormones, however, are not affected by GH treatment. In addition to IGF-1 and IGFBP-3, levels of the hormones listed in Table 2, which also have been found to decline as part of normal aging, should be monitored and treated as needed.

Level 3. DNA analysis. Biomarkers on the chromosomal level are currently being developed and include telomere position and DNA strand breakage rates. A breakthrough blood test can track damage to the DNA to assess the effect a GH regimen is having on reducing damage to DNA.

Assessment of Growth Hormone Deficiency in Adults Questionnaire. The Assessment of Growth Hormone Deficiency in Adults Questionnaire can be a useful complement to the clinical evaluation of patients with GH deficiency.[53]

Proper dosage. The aim of wellness-oriented physicians is to help their patients with GH deficiency optimize levels of essential hormones. Customizing the proper dosage for each individual patient is accomplished through regular clinical examinations and laboratory testing. The final decision to treat adults with GH-deficiency requires thoughtful clinical judgment with a careful evaluation of the benefits and risks specific to the individual.[49]

When the correct physiologic dosage is properly determined and monitored by a qualified physician, adverse effects of GH replacement therapy in adult patients are minor and self-limited (side effects disappear by decreasing the dosage or ceasing treatment). The side-effect profile generally does not apply to clinical treatment where low doses are used initially and doses are slowly ramped up or decreased if side effects occur. Also, when the same total dose is divided daily over a week (instead of administered 3 days a week), side effects are diminished or absent.[54]

One approach to titrating the dosage to an individual's optimal level is to use end-results based on patient symptomatology (eg, patient's energy, physique, mood, cardiovascular measures, blood pressure, cholesterol) and monitor IGF-1 levels to be sure they remain within a physiological range. Hopefully, in the future, IGF-1 levels will be monitored during an individual's prime years as a means of determining his or her personal ideal IGF-1 level.

Route of administration. Individual patients typically self-administer approximately 1 unit of GH in the subcutaneous tissue of the anterior thigh or lower abdomen via an insulin syringe every evening (or 6 nights a week) at bedtime.

Regulatory Issues[39,45,54]

Physicians can legally prescribe GH to patients who have a deficiency of this hormone. The definition of "deficiency" has been open to interpretation. As mentioned, stimulation tests are commonly utilized for this purpose; however, one can be led astray by treating a lab result rather than the patient's clinical symptoms.**History.** Synthetic anabolic steroid hormones, such as those abused by some professional athletes and body builders looking for an "edge," have been incorrectly

confused with the physician-supervised prescription of GH for deficient adults (partly because GH is also similarly misused).

The 1988 federal law 21 U.S.C. § 333(e), a provision of the Food, Drug, and Cosmetic Act (FDCA), states: "Whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by [the FDA] and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison." We need to take a critical look at the historical context and legislative intent of this law before interpreting it. The law did not originally address human GH but was written and passed with respect to anabolic steroids. The legislative history of the law's creation shows intent to focus on steroid trafficking to athletes, particularly adolescent athletes, amid increasing reports of amateur and professional sports doping.

Heightened alarm over steroids and human GH in athletics resulted in the Anabolic Steroid Control Act of 1990. This Act moved steroids from the FDCA to the Controlled Substances Act. At this time, Congress was presented with the option of making human GH a controlled substance as well. Following expert medical testimony that human GH lacks the adverse psychological and physical effects of steroids, Congress chose, nonetheless, to replace "steroids" with "human growth hormone" in the FDCA law originally drafted to stop trafficking to cheating athletes.

In adults, the FDA has stated that distribution of GH is legal for two conditions: wasting syndrome of AIDS and AGHD. For the legal distribution of GH in AGHD, two diagnostic criteria must be met: 1) patients must have a biochemical diagnosis of AGHD by means of a subnormal response to the standard GH stimulation test (peak GH, < 5.0 ng/L) and 2) patients must have AGHD either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma or patients must have been GH deficient during childhood. The stimulation test for GH deficiency is performed with GH-releasing hormone (or factor), arginine, glucagons, or insulin-induced hypoglycemia.

Section 303 (f) (1) of the FDCA permits distribution of GH in connection with "treatment of a disease" or "other recognized medical condition." Nothing in this statute dictates to physicians how to diagnose the indications for diseases that may be treated by human GH. Since 1996, hormone replacement in adults with clinically diagnosed GH deficiency constitutes a treatment of a disease and is therefore medically authorized.

Next Steps

ClinicalTrials.gov review. In November 2007, we searched the Web site, ClinicalTrials.gov, using the search term "human growth hormone." This search resulted in 106 clinical trials registered on the site. Narrowing down the search using the term "adult human growth hormone deficiency" resulted in 24 studies of which 22 are currently recruiting subjects. Of the 24 studies listed as "adult" studies, 5 are actually clinical trials with children or adolescents.

Conditions being investigated for the effects of GH include bone loss in men, GH deficiency, GH deficiency in young adults age 18–35 years, cardiovascular risk, traumatic brain injury, adults with low GH who survived childhood cancer where treatment caused low bone density, and fibromyalgia. Five clinical trials for patients with HIV infection were designed to investigate the effects of human GH therapy on the following conditions: HIV infections, lipodystrophy, insulin resistance, metabolic syndrome X, body weight changes, and diabetes.

Only 1 of the 24 studies addresses the elderly population. This study will evaluate the independent effects and interaction of human GH and testosterone in 108 men age 65–90 years who were identified as being deficient in those two hormones. This clinical trial began enrolling subjects in September 2002 at Tufts University (Boston, Mass) and Washington University School of Medicine (Saint Louis, Mo) and was scheduled for completion in April 2007 but still is listed on ClinicalTrials.gov as recruiting subjects.

We repeated the search on ClinicalTrials.gov in August 2008 using the same terms. Interestingly, there are now 373 clinical trials registered using the term "human growth hormone." The repeated search using the term "adult human growth hormone deficiency" resulted in 41 studies of which 22 studies are recruiting children and adolescents only and 2 studies were limited to the elderly population.

Additional research. Prospective, randomized, multicenter, clinical trials that enroll and follow large numbers of adult and elderly patients who are hormone deficient over the course of many years are needed to overcome limitations of previous studies (most notably short duration and inadequate or incomplete follow-up) and to resolve remaining contradictory research findings and scientific disputes with respect to the effects of human GH on health outcomes.

A team of internationally renowned research scientists has already assembled to complete a full clinical research protocol to further study human GH on adults. The trial's design will include randomization, treatment comparison groups, uniform study eligibility criteria, evidence-based diagnostic measures, and standardized outcome variables. The study will be conducted under proper regulatory oversight and abide by the Code of Federal Regulations (Title 21 CFR). Protected health information will be assessed in accordance with the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA), Title 45, US Code of Federal Regulations 164.501, 164.508, and 164.512.

Conclusion

Although human GH is not "a fountain of youth," it has tremendous promise for treating adults whose pituitary glands release insufficient amounts of GH. This includes people in the fastest growing segment of the population—those over 65 years of age. Replacing essential hormones that decline with age may be as important as replacing insulin for people with diabetes. The benefits of GH therapy, moreover, can be maximized when included in a broader, comprehensive treatment program that includes balancing other hormones as well as modifying diet and physical activity based on each patient's unique medical profile.

While studies, new and old, provide convincing evidence that GH enhances health and quality of life, skepticism remains with respect to the benefits of GH treatment. To provide reassurance that GH can be a safe and necessary form of hormone replacement therapy for adults with GH deficiency, the accumulation of long-term treatment data is required.[55]

A new clinical trial whose methodological design will allow for a large enough sample size and a long enough follow-up period will help develop objective answers to some remaining scientific disagreements on the value of human GH for adults. ■

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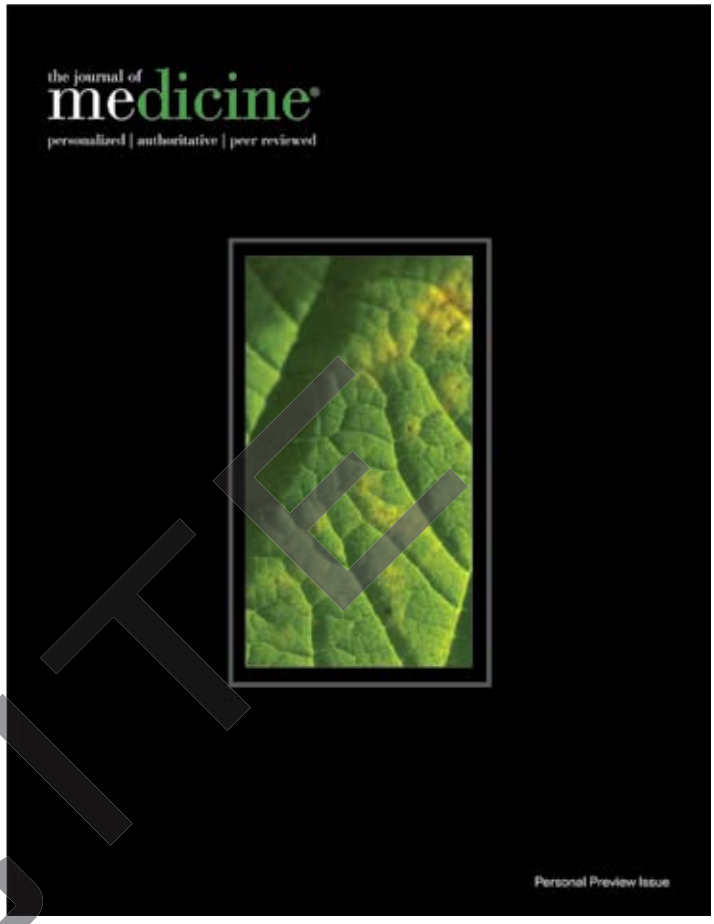

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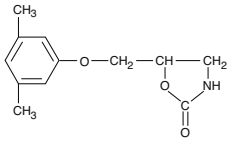
SKELAXIN®
(Metaxalone) Tablets

DESCRIPTION

SKELAXIN® (metaxalone) is available as an 800 mg oval, scored pink tablet.

Chemically, metaxalone is 5-[(3,5- dimethylphenoxy) methyl]-2-oxazolidinone. The empirical formula is $C_{12}H_{15}NO_3$, which corresponds to a molecular weight of 221.25. The structural formula is:



Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble in ether or water.

Each tablet contains 800 mg metaxalone and the following inactive ingredients: alginic acid, ammonium calcium alginate, B-Rose Liquid, corn starch and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Pharmacokinetics:

The pharmacokinetics of metaxalone have been evaluated in healthy adult volunteers after single dose administration of SKELAXIN under fasted and fed conditions at doses ranging from 400 mg to 800 mg.

Absorption

Peak plasma concentrations of metaxalone occur approximately 3 hours after a 400 mg oral dose under fasted conditions. Thereafter, metaxalone concentrations decline log-linearly with a terminal half-life of 9.0 ± 4.8 hours. Doubling the dose of SKELAXIN from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C_{max}) and area under the curve (AUC).

Dose proportionality at doses above 800 mg has not been studied. The absolute bioavailability of metaxalone is not known.

The single-dose pharmacokinetic parameters of metaxalone in two groups of healthy volunteers are shown in Table 1.

Table 1: Mean (%CV) Metaxalone Pharmacokinetic Parameters

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC_∞ (ng·h/mL)	$t_{1/2}$ (h)	**CL/F** (L/h)
400[1]	983 (53)	3.3 (35)	7479 (51)	9.0 (53)	68 (50)
800[2]	1816 (43)	3.0 (39)	15044 (46)	8.0 (58)	66 (51)

[1]Subjects received 1x400 mg tablet under fasted conditions (N=42)

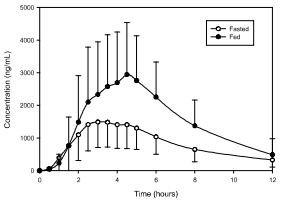
[2]Subjects received 2x400 mg tablets under fasted conditions (N=59)

Food Effects

A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg SKELAXIN tablet under fasted conditions and following a standard high-fat breakfast. Subjects ranged in age from 18 to 48 years (mean age = 23.5 ± 5.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 177.5% and increased AUC (AUC_{0-t}, AUC_∞) by 123.5% and 115.4%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.3 h *versus* 3.3 h) and terminal half-life was decreased (2.4 h *versus* 9.0 h) under fed conditions compared to fasted.

In a second food effect study of similar design, two 400 mg SKELAXIN tablets (800 mg) were administered to healthy volunteers (N=59, 37 males, 22 females), ranging in age from 18-50 years (mean age = 25.6 ± 8.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 193.6% and increased AUC (AUC_{0-t}, AUC_∞) by 146.4% and 142.2%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.9 h *versus* 3.0 h) and terminal half-life was decreased (4.2 h *versus* 8.0 h) under fed conditions compared to fasted conditions. Similar food effect results were observed in the above study when one SKELAXIN 800 mg tablet was administered in place of two SKELAXIN 400 mg tablets. The increase in metaxalone exposure coinciding with a reduction in half-life may be attributed to more complete absorption of metaxalone in the presence of a high fat meal (Figure 1).

Figure 1. Mean (SD) Concentrations of Metaxalone following an 800 mg Dose under Fasted and Fed Conditions



Distribution, Metabolism, and Excretion

Although plasma protein binding and absolute bioavailability of metaxalone are not known, the apparent volume of distribution (V/F ~ 800 L) and lipophilicity (log P = 2.42) of metaxalone suggest that the drug is extensively distributed in the tissues. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites.

Pharmacokinetics in Special Populations

Age: The effects of age on the pharmacokinetics of metaxalone were determined following single administration of two 400 mg tablets (800 mg) under fasted and fed conditions. The results were analyzed separately, as well as in combination with the results from three other studies. Using the combined data, the results indicate that the pharmacokinetics of metaxalone are significantly more affected by age under fasted conditions than under fed conditions, with bioavailability under fasted conditions increasing with age.

The bioavailability of metaxalone under fasted and fed conditions in three groups of healthy volunteers of varying age is shown in Table 2.

Table 2: Mean (%CV) Pharmacokinetics Parameters Following Single Administration of Two 400 mg SKELAXIN Tablets (800 mg) under Fasted and Fed Conditions

	Younger Volunteers		**Older Volunteers**			
Age (years)	25.6 ± 8.7		39.3 ± 10.8		71.5 ± 5.0	
N	59		21		23	
Food	Fasted	Fed	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL)	1816 (43)	3510 (41)	2719 (46)	2915 (55)	3168 (43)	3680 (59)
T_{max} (h)	3.0 (39)	4.9 (48)	3.0 (40)	8.7 (91)	2.6 (30)	6.5 (67)
AUC_{0-t} (ng·h/mL)	14531 (47)	20683 (41)	19836 (40)	20482 (37)	23797 (45)	24340 (48)
AUC_∞ (ng·h/mL)	15045 (46)	20833 (41)	20490 (39)	20815 (37)	24194 (44)	24704 (47)

Gender: The effect of gender on the pharmacokinetics of metaxalone was assessed in an open label study, in which 48 healthy adult volunteers (24 males, 24 females) were administered two SKELAXIN 400 mg tablets (800 mg) under fasted conditions. The bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL *versus* 1335 ng/mL) and AUC_∞ (17884 ng·h/mL *versus* 10328 ng·h/mL). The mean half-life was 11.1 hours in females and 7.6 hours in males. The apparent volume of distribution of metaxalone was approximately 22% higher in males than in females, but not significantly different when adjusted for body weight. Similar findings were also seen when the previously described combined dataset was used in the analysis.

Hepatic/Renal Insufficiency: The impact of hepatic and renal disease on the pharmacokinetics of metaxalone has not been determined. In the absence of such information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment.

INDICATIONS AND USAGE

SKELAXIN (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Known hypersensitivity to any components of this product.

Known tendency to drug induced, hemolytic, or other anemias.

Significantly impaired renal or hepatic function.

WARNINGS

SKELAXIN may enhance the effects of alcohol and other CNS depressants.

PRECAUTIONS

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients section).

Information for Patients

SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

Drug Interactions

SKELAXIN may enhance the effects of alcohol, barbiturates and other CNS depressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of metaxalone has not been determined.

Pregnancy

Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in children 12 years of age and below have not been established.

ADVERSE REACTIONS

The most frequent reactions to metaxalone include:

CNS: drowsiness, dizziness, headache, and nervousness or "irritability";

Digestive: nausea, vomiting, gastrointestinal upset.

Other adverse reactions are:

Immune System: hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia; hemolytic anemia;

Hepatobiliary: jaundice.

Though rare, anaphylactoid reactions have been reported with metaxalone.

OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with alcohol.

When determining the LD_{50} in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD_{50} could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

Treatment - Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day.

HOW SUPPLIED

SKELAXIN (metaxalone) is available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Available in bottles of 100 (NDC 60793-136-01) and in bottles of 500 (NDC 60793-136-05).

Store at Controlled Room Temperature, between 15°C and 30°C (59°F and 86°F).

Rx Only

Prescribing Information as of April 2007.

King Pharmaceuticals

Distributed by: King Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Mallinckrodt Inc., Hobart, NY 13788