Application of the Yasko Protocol to the Treatment of Chronic Fatigue Syndrome

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Disclaimers

1. People undergoing treatment for chronic fatigue syndrome as discussed in this talk must be under the care of a licensed physician.

2. Some of what will be discussed in this talk is hypothesis—unproven theory. I will try to distinguish between what is hypothesis and what is well established and considered to be scientifically true at this time.

3. The authors have no financial interest in the tests or supplements discussed in this paper.

The Bottom Line

- A hypothesis has been developed to explain chronic fatigue syndrome (CFS).
- Key features: a chronic partial block of the methylation cycle, significant draining of folate from the cells, and a chronic depletion of glutathione.
- Explains: genetic predisposition, biochemical abnormalities, and many seemingly unconnected symptoms of CFS.
- Tested in a clinical study using a simplified treatment extracted from the full treatment program of Dr. Amy Yasko, and results are found to be consistent with the hypothesis.
- Lab testing is available to determine whether the hypothesis applies to a particular patient. So far it appears to apply to most CFS patients.
- This simplified Yasko treatment is currently producing significant benefits in most patients who use it, and it has resulted in apparently complete recovery in a small number of patients.

Topics to be covered in this talk

- What is chronic fatigue syndrome (CFS)?
- What is the history of CFS?
- Who has CFS?
- What is glutathione, and what does it do?
- What is the methylation cycle, and what does it do?
- What is the Glutathione Depletion—Methylation Cycle Block hypothesis for CFS?
- Why doesn't everyone get CFS?
- Why do more women than men get CFS?
- How does the GD-MCB hypothesis account for the features of CFS?
- Why and how has the Yasko protocol been applied to treating CFS?
- What clinical testing has been done and what were the results?
- What testing is available to find out if the GD-MBC hypothesis applies to a given case of CFS?

What is chronic fatigue syndrome?

- Defined in terms of a set of symptoms, and diagnosed when other possible causes for them have been ruled out.

- Symptoms: Severe chronic lack of energy, post-exertional exhaustion, difficulties in thinking and memory, pain especially in the muscles, sleep problems, immune system problems, endocrine problems, and many, many more.

- Case definitions:

  Fukuda et al.(1994): CDC-sponsored international research definition

  Carruthers et al.(2003): Canadian consensus diagnostic definition

What is chronic fatigue syndrome? (continued)

- Many people are unhappy with the name or with the definitions, or both. They believe that the name trivializes a very serious illness, and that the definitions in terms of symptoms are not specific enough. There is no diagnostic biomarker, and the cause (or causes) are not known/agreed upon. The definitions produce a heterogeneous population.

- How is fibromyalgia related to CFS?

  The original diagnostic definition for fibromyalgia from the American College of Rheumatology focused on pain and pain sensitivity. Many people satisfied the definitions for both CFS and fibromyalgia, but others did not. The proposed new definition moves fibromyalgia closer to overlapping with CFS. The cause of fibromyalgia is likewise not known.

What is chronic fatigue syndrome ? (continued)

- Is it the same disorder as myalgic encephalomyelitis (M.E.), which originated in the UK? There is disgreement about this.

- Does CFS have a sudden or a gradual onset? There are some cases of each.

- Does CFS occur in epidemics or clusters, or does it occur sporadically? Some of each.

- What's the severity of CFS?

  Some people with CFS are able to continue working full time, some carry on a few normal activities, some are housebound, some are bedridden, and a few even die from it, though the cause of death may be assigned to something more immediate. Most people who develop CFS are chronically ill for many years.

What is the history of CFS?

- First defined in the U.S. by the CDC in 1989, after clusters of cases appeared at a few locations, the best-known being near Incline Village on Lake Tahoe in Nevada.

- CFS had probably existed for much longer, but under different names.

- It seems that the prevalence has been much higher starting in the 1980s, but this is difficult to prove.

- Cause or causes have not been found (or agreed upon). The most recent suspect is the XMRV retrovirus.

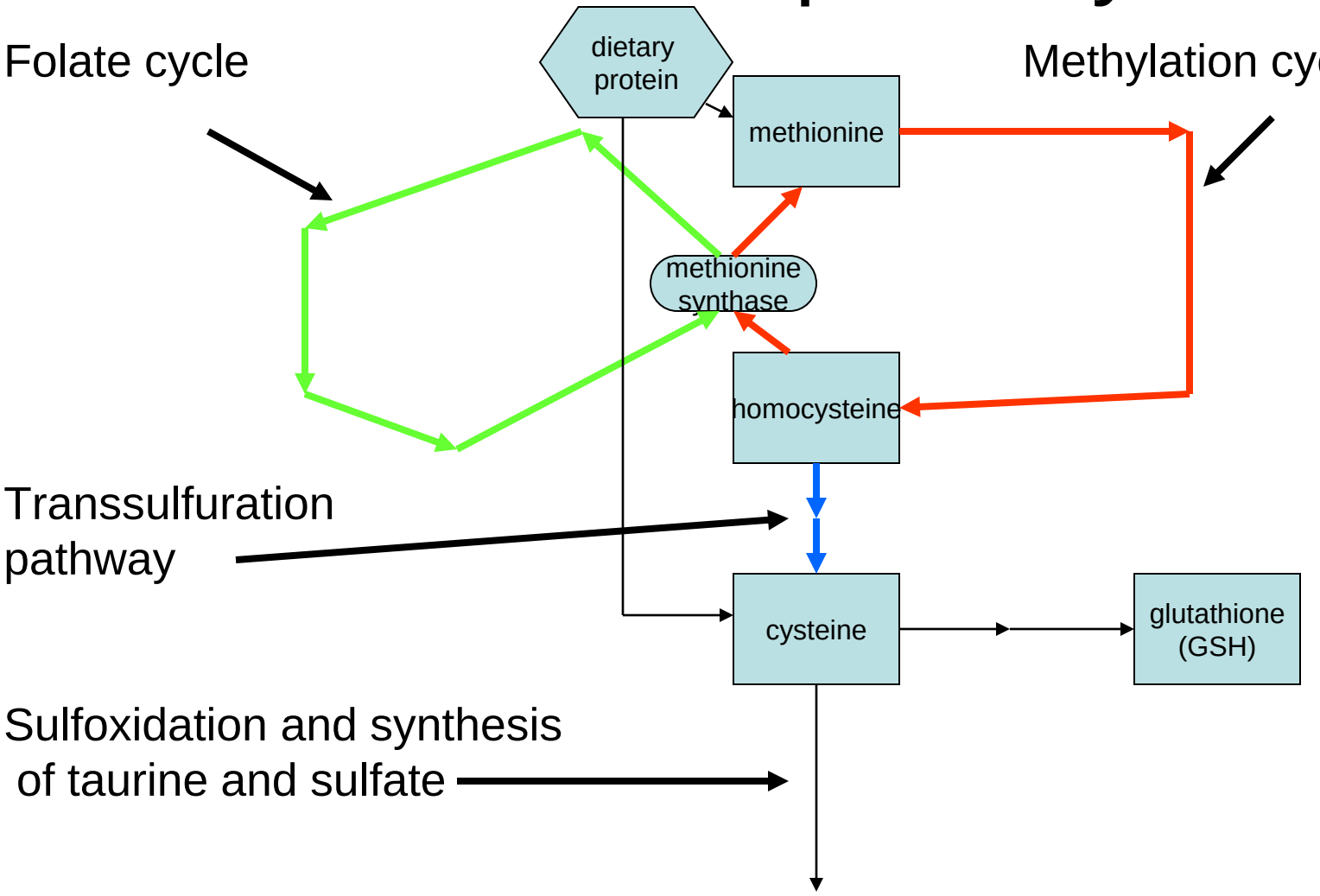
Who has chronic fatigue syndrome?

- A million or more people in the U.S., and several million more worldwide.
- More women than men.
- Some children, but mostly adults.
- Minorities have higher prevalences than the non-minority population.
- Only about 15% of those in the U.S. who have CFS are believed to have been diagnosed.

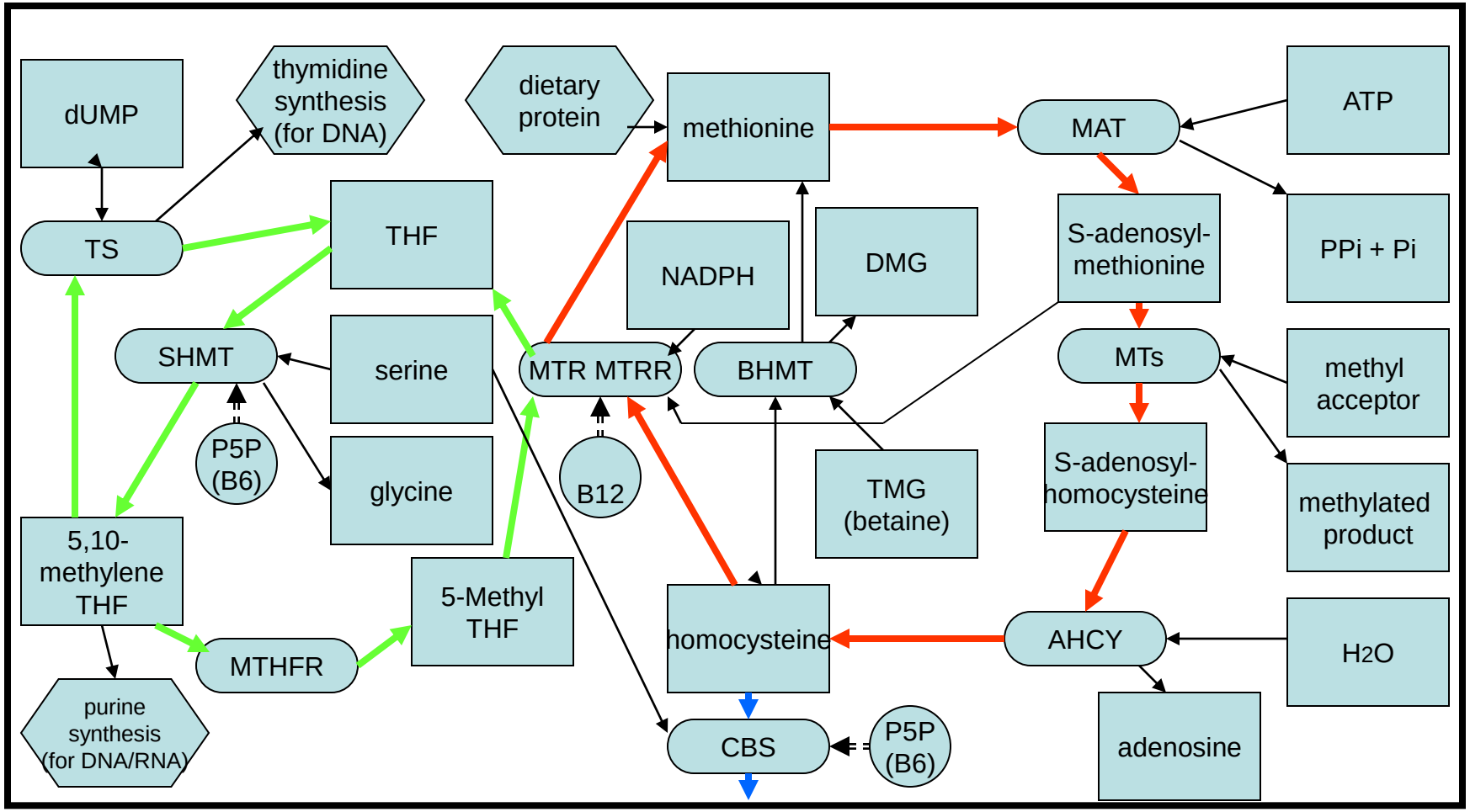
Glutathione—What is it and what does it do?

- A tripeptide, composed of glutamate, cysteine and glycine
- Found in all cells, blood, bile and epithelial lining fluid of the lung
- Synthesized by cells, particularly liver and red blood cells
- The most abundant thiol (sulfhydryl)-containing substance in cells
- Has reduced and oxidized forms, GSH and GSSG
- Ratio of GSH to GSSG controls the redox potential in cells
- Serves as basis for the antioxidant system, quenching reactive oxygen species
- Conjugates several classes of toxins for removal from the body in Phase II detox, and quenches free radicals generated in Phase I detox in general
- Supports immune system, especially cell-mediated immunity
- Plays important role in synthesis of proteins that contain cysteine
- Participates in bile production
- Protects vitamin B12 inside the cells

Methylation cycle and associated biochemical pathways

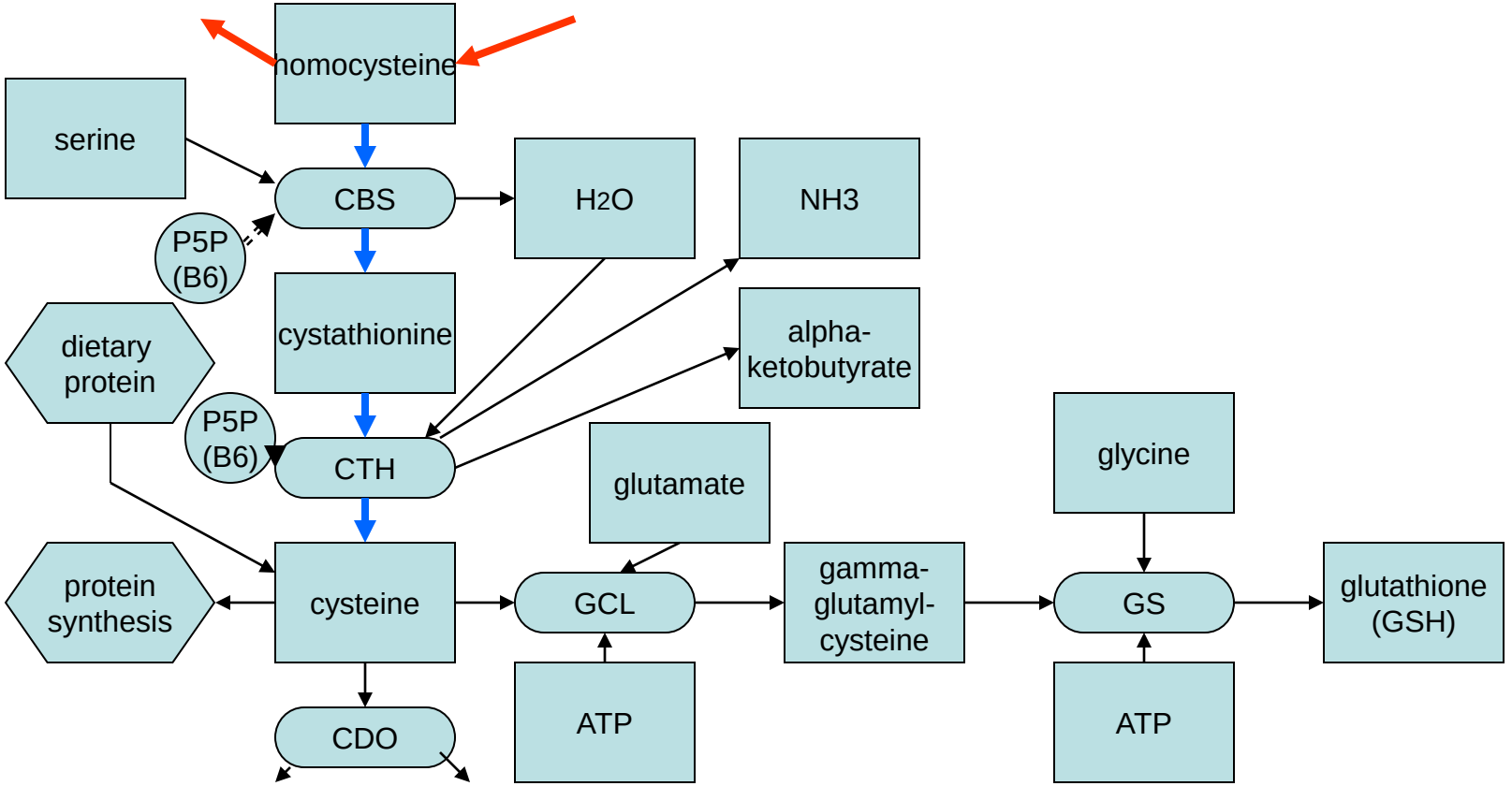


(combined) Methylation and Folate cycles (showing link to transsulfuration pathway via CBS)

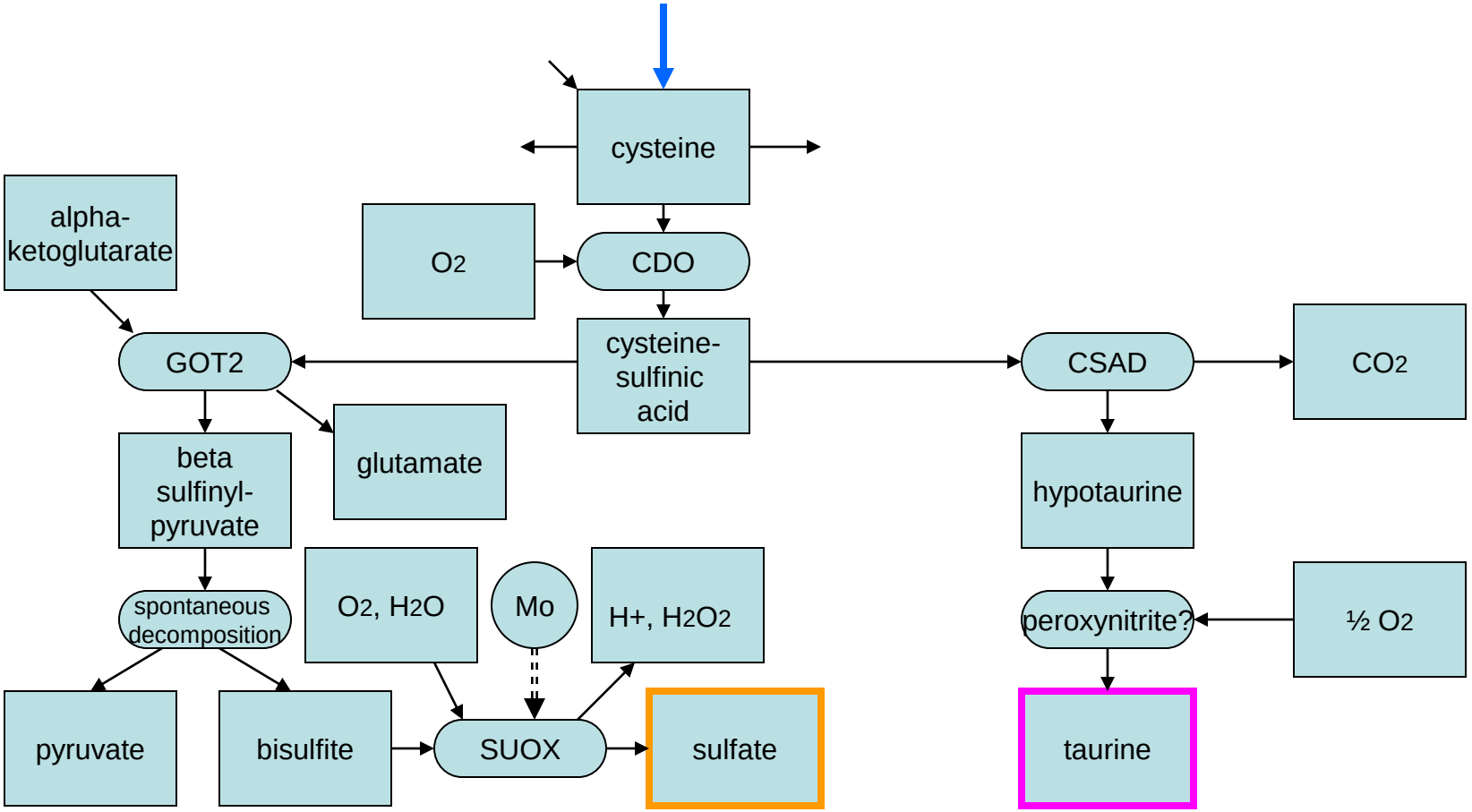


Transsulfuration pathway

[Note that a complete transsulfuration pathway is found only in cells of the liver, kidneys, pancreas, intestine, lens of the eye, and (at much lower capacity) the brain.]



Sulfoxidation and synthesis of sulfate and taurine



What does the methylation cycle do?

- Supplies methyl (CH3) groups for a large number of biochemical reactions in the body.

- Controls the overall sulfur metabolism, balancing the needs for methyl groups, for GSH to control oxidative stress, and for other sulfur metabolites, including cysteine, taurine and sulfate.

- Coordinates the production of new DNA with the supply of methyl groups, which are used to methylate DNA, among many other roles.

What causes most cases CFS, according to this hypothesis?

Genetic predisposition

together with:

Stressors

(Some combination of a variety of physical, chemical, biological and or psychological/emotional stressors, the particular combination differing from one case to another).

This combination initially raises cortisol and epinephrine, and it depletes intracellular reduced glutathione (GSH).

Pathogenesis (disease development) of most cases of CFS, according to this hypothesis

1. Stressors deplete glutathione (GSH), which produces oxidative stress, allows toxins to accumulate, and removes protection from vitamin B12.

2. Oxidative stress partially blocks methionine synthase in the methylation cycle.

3. Accumulated toxins (probably especially mercury) react with much of the vitamin B12.

4. The partial block of methionine synthase (MTR) becomes chronic, and the sulfur metabolism therefore becomes dysregulated.

Pathogenesis (continued)

5. Sulfur metabolites drain down the transsulfuration pathway and are eventually excreted, depleting methionine.

6. Intracellular cysteine levels become too low to restore glutathione levels to normal.

7. Glutathione depletion and the partial block in methionine synthase form a vicious circle, and this vicious circle becomes chronic, producing CFS.

8. The symptoms of CFS result from this vicious circle.

Why doesn’t everyone get CFS?

- A major reason is likely to be differences in the combinations of inherited genetic polymorphisms.
- There has not yet been a complete genome study of the polymorphisms that are more frequent in CFS than in the general population.
- However, there is evidence from family and twin studies as well as from limited polymorphism studies that there is a genetic component in the development of CFS.

What are some things that might be expected if glutathione were depleted, and are they observed in CFS?

- Oxidative stress—observed.
- Mitochondrial dysfunction and low ATP output, leading, for examples, to physical fatigue in skeletal muscles—observed; and diastolic dysfunction in the heart, leading to low cardiac output—observed.
- Buildup of toxins, including heavy metals—observed.
- Immune response shift to Th2—observed.
- Inability of T cells to proliferate in response to mitogens—observed.
- Reactivation of herpes family viral infections—observed.
- Thyroid problems—observed.
- Low secretion and dysregulation of certain cysteine-containing secretory proteins, including ACTH, antidiuretic hormone, and perforin.

    Low ACTH leads to blunting of the HPA axis—observed, low antidiuretic hormone leads to high daily urine volumes and constant thirst—observed, and low perforin leads to low cytotoxic activity of the natural killer cells and the CD8 (“killer”) T cells—observed.

What are some things that might be expected if the methylation capacity were diminished, and are they observed in CFS?

- Overexpression of many genes because of lack of gene silencing by methylation—observed.
- Lowered synthesis of choline and creatine—abnormal ratio of choline to creatine observed in brain.
- Lowered synthesis of carnitine—deficit observed.
- Lowered synthesis of coenzyme Q-10—supplementation observed to be beneficial.
- Lowered synthesis of three component of myelin—slow brain processing speed observed.

How does this hypothesis account for the higher prevalence of CFS in women than in men?

- During their potentially reproductive years, estrogens are produced in larger amounts in women, and must be metabolized.
- Some people (both men and women) inherit polymorphisms in the genes that code for some of the detox enzymes involved in the metabolism of the estrogens (CYP1B1, COMT and GST enzymes).
- In women, these polymorphisms can lead to redox cycling when metabolizing estrogens. This adds an additional bias toward depletion of glutathione and development of oxidative stress.
- Oxidative stress initiates the pathogenesis of CFS.

Why was the Yasko protocol applied to CFS?

- CFS involves glutathione depletion, as was found in autism, and it appeared that this depletion could not be corrected by direct boosting of glutathione.
- It seemed that there was a good chance that CFS also involved a partial block in the methylation cycle, as was found in autism.
- If so, treatments that were effective for treating the methylation cycle issues in autism might also be effective for CFS.
- The Yasko protocol was directed toward treating the methylation cycle and was being successfully applied to autism.

How was the Yasko protocol applied to CFS?

- Two ways: the complete treatment protocol was tried initially and is still used by some patients, and a “simplified treatment approach” was introduced later.

- What is the simplified treatment approach?

  Five supplements extracted from Step 2 of the complete Yasko treatment protocol: Perque Activated B12 Guard (hydroxocobalamin), FolaPro (5-methyl tetrahydrofolate), Intrinsi B12/folate: (Combination of [folic acid, 5-methyl tetrahydrofolate, and folinic acid], cyanocobalamin, calcium, phosphorus, and intrinsic factor), phosphatidyl serine complex, and General Vitamin Neurological Health Formula. [Note that Intrinsi/B12/folate has since been replaced by Actifolate.]

- Why was this simplified approach used? To decrease the cost and the complexity, which are problems for many CFS patients, who are unable to work, and have cognitive problems as a result of this disorder. Many were not able to use the full treatment protocol.

- Were there disadvantages to simplifying the treatment? Yes, it was a compromise.

Who influenced the history of applying the Yasko protocol to the treatment of CFS?

- Paul Cheney, M.D., Patricia Salvato, M.D., Derek Enlander, M.D.
- Michael Goldberg, M.D., Prof. Malcolm Hooper
- Bernard Rimland, Ph.D.
- S. Jill James, Ph.D.
- Prof. Richard Deth
- S.R. (patient)
- Amy Yasko, Ph.D., N.D.
- S.T. (patient)
- David Bell, M.D.
- K.T. (patient)
- L.D. (patient)
- Tapan Audhya, Ph.D.
- Ratna Ling Working Group
- Neil Nathan, M.D.

Clinical Study of Simplified Yasko Protocol for CFS/fibromyalgia

- Type: Open-label clinical study
- Setting: A single private practice in Springfield, Missouri
- Informed consent: Patients signed forms after explanation of the study and its possible risks.
- Duration of treatment: Six months (However, note that after the 6-month study period, individualized treatments were added to the basic protocol for an additional 3 months.)
- Outcome measures: Objective testing and self-rating of symptoms (Details are given later in this paper.)
- Restrictions on medications and additional supplements: None, except that they and their dosages were not to be changed during the study without the knowledge and agreement of one of us (NN**).**

Patients in the Clinical Study

- Total number--30. All suffered from chronic fatigue.
- Twenty-one met our strict criteria for CFS (Fukuda plus postexertional fatigue and malaise), and a statistical analysis was performed on their results from six months of treatment. This can be found at www.cfsresearch.org
- Of these 21 patients, 18 also met the ACR criteria for fibromyalgia.
- Sex: All female
- Ethnicity: All Caucasian
- Ages: 33 to 84 (mean—52) years
- Durations of illness: 1 to 20+ years
- Histories of previous treatment: These patients had exhibited partial response to treatment ranging from one to twelve years in duration with a protocol that included evaluation and treatment of adrenal, thyroid and sex hormones; food allergies; intestinal dysbiosis; heavy metal toxicity; infections (EBV, Lyme disease, mycoplasma); mold exposure; magnesium deficiency; and other nutritional imbalances

Patients in the Clinical Study (continued)

Additional diagnoses:

- Migraine headaches—15 patients
- Irritable bowel syndrome—13
- Chronic sinus infections—11
- Endometriosis—6
- Restless leg syndrome—5
- Mononucleosis (Epstein—Barr virus)—5
- Mold exposure and/or toxicity—5
- Multiple chemical sensitivity—4
- Lyme disease (previously treated)—2
- Interstitial cystitis—1
- Mycoplasma infections—1
- Chronic vulvitis—0

Initial General Questionnaire

The patients were given an initial questionnaire that requested the following information:

- Starting date of treatment
- Name
- Age
- Date of birth
- Sex
- Family history of these conditions (yes or no?), if so, which relatives?
- Date of onset of symptoms
- Sudden onset (yes or no?)
- Cause of onset, if known
- Date of diagnosis of chronic fatigue
- Date of diagnosis of fibromyalgia
- Other diagnoses (listed in previous section above)
- Current medications
- Current supplements

The initial general questionnaire also included questions to ascertain whether the patients met the Fukuda et al. case definition for CFS and the ACR criteria for fibromyalgia, and whether they had experienced post-exertional fatigue and malaise.

Supplement Protocol

The treatment protocol used in this study was extracted from the full treatment program developed by Yasko for the treatment of autism and adult neurological diseases. It consisted of five supplements:

- FolaPro (5-methyl tetrahydrofolate): ¼ tablet (200mcg) daily
- Intrinsi B12/folate: ¼ tablet daily (Combination of [folic acid, 5-methyl tetrahydrofolate, and folinic acid] (200 mcg), cyanocobalamin (125 mcg), calcium (22.5 mg), phosphorus (17.25 mg), and intrinsic factor (5 mg))
- General Vitamin Neurological Health Formula (a multivitamin, multimineral supplement including antioxidants, trimethylglycine, nucleotides, supplements to support the sulfur metabolism, a high ratio of magnesium to calcium, and no iron or copper): starting with ¼ tablet and increasing the dosage as tolerated, to 2 tablets daily
- Phosphatidyl Serine Complex (phospholipids and fatty acids): 1 softgel capsule daily
- Activated B12 Guard (hydroxocobalamin): 1 sublingual lozenge (2,000 micrograms) daily

Composition of General Vitamin Neurological Health Formula

- Serving Size: 6 Tablets (note that up to 2 tablets per day are used in the treatment)

- **Amount per serving:** Vitamin A (as palmitate)5000 IU,Vitamin C (ascorbic acid)500 mg,Vitamin D (as cholecaliciferol)400 IU,Vitamin E (as d-alpha tocopheryl succinate)400 IU,Vitamin K (as phytonadione)40 mcg,Vitamin B-1 (as benfotiamine)25 mg,Vitamin B-2 (as riboflavin)12.5 mg,Niacin (as niacinamide)37.5 mg,Vitamin B-6 (as pyridoxal-5-phosphate)12.5 mg,Folic Acid100 mcg,Vitamin B-12 (cyanocobalamin B12)250 mcg,Biotin150 mcg,Pantothenic Acid (as d-calcium pantothenate)50 mg,Calcium (as calcium d-glucarate)25 mg,Magnesium (as citrate, oxide)100 mg,Zinc (as monomethionine)5 mg,Selenium (as L-selenomethionine)100 mcg,Manganese (as arginate)1 mg,Chromium (as polynicotinate)100 mcg,Molybdenum (as amino acid chelate)75 mcg,Potassium (as citrate)5 mg,Broccoli florets powder160 mg,Citrus bioflavonoids50 mg,Choline (as bitartrate)25 mg,Inositol25 mg,PABA (para-amino benzoic acid)5 mg,Garlic (Allium sativum) bulb powder200 mg,L-methionine150 mg,Milk thistle (Silybum marianum) seed extract100 mg,N-acetyl-cysteine75 mg,Pine (Pinus maritimus) bark extract25 mg,Taurine250 mg,Turmeric (Curcuma longa) root extract50 mg,Intrinsic Factor5 mg,Trimethylglycine (TMG)50 mg, Free Form Nucleotide Complex100 mg,Boron1 mg,L-Carnitine (Tartrate)100 mg.

- (Ref.: http://www.holisticheal.com)

Objective Testing: Methylation Pathways Panel from Health Diagnostics and Research Institute (formerly Vitamin Diagnostics, Inc.)

Metabolites measured:

- S-adenosylmethionine (red blood cells)
- S-adenosylhomocysteine (red blood cells)
- Adenosine (plasma)
- 5-methyl tetrahydrofolate (plasma)
- 10-formyl tetrahydrofolate (plasma)
- 5-formyl tetrahydrofolate (folinic acid) (plasma)
- Tetrahydrofolate (plasma)
- Folic acid (plasma)
- Folinic acid (whole blood)
- Folic acid (red blood cells)
- Glutathione (GSH) (plasma)
- Oxidized glutathione (GSSG) (plasma)

Additional Objective Testing

- Thyroid panel (TSH, total T4, total T3)
- Characterization of polymorphisms associated with the methylation cycle: (AHCY-01, BHMT-08, CBS C699T, COMT V158M, and MTR A2756G)
- Human Leukocyte Antigen (HLA) DR DQ typing
- Functional Acuity Contrast Testing (FACT)
- C4a
- TGF beta-1

Enumeration of Symptoms and Self-Rating of Outcome Measures

- The patients were asked to mark their symptoms on a checklist (initially and at 6 months) that included 38 symptoms.

- The patients were also asked to rate five outcome measures initially and at 3 and 6 months on visual analog scales ranging from 1 to 10. These measures consisted of energy, sleep, mental clarity, freedom from pain, and overall feeling of wellbeing.

- In addition, at 3 and 6 months they were asked to estimate their percentage of improvement.

Symptoms Checklist

- Confusion, disorientation
- Difficulty in word finding
- Impairment of concentration, difficulty assimilating new
- information
- Reduced task completion
- Hypersensitivity to bright light
- Night blindness
- Tearing, redness of eyes
- Blurred vision
- Chronic aching muscles
- Joint pain, morning joint stiffness
- Pain in weight bearing joints
- Nausea
- Loss of appetite
- Weight gain (How much, and over what period of time?)
- Abdominal pain
- Chronic sinus congestion
- Chronic cough that mimics asthma

Symptoms Checklist (continued)

- Shortness of breath
- Ice-pick like pain, or electrical pain that shoots into a muscle
- Nosebleeds
- Metallic taste or other unusual taste
- Vertigo, dizziness
- Ringing in the ears (tinnitus)
- Rage or inappropriate anger
- Panic attacks or anxiety
- Depression
- Tingling, “needles and pins” sensation
- Increased sensitivity to touch
- Difficulty with sleep
- Difficulty with getting to sleep
- Difficulty with staying asleep
- Mood swings
- Excessive thirst or frequent urination
- Impotence
- Irregular vaginal bleeding
- Low body temperature
- Chronic yeast infections
- Onset of menopause (if appropriate)

Conduct of the Clinical Study

- The clinical study was conducted by one of us (NN) in his private practice, with the help of administrative and nursing staff.
- The study was explained to each of the patients, including the purposes, the protocol, and the possible risks. Each patient signed an informed consent and responded to the initial general questionnaire.
- The patients were supplied with the supplements in the protocol at cost.
- The objective testing as described above was performed on the patients initially and after 3 and 6 months of treatment. After 3 and 6 months of treatment, they also responded to follow-up questionnaires that included general questions about response to treatment, a symptom checklist and self-rated visual analog scales for the outcome measures described earlier.

AFTER 6 MONTHS

WE CONTINUED THE METHYLATION SUPPLEMENTATION PROGRAM AND ADDED INDIVIDUAL TREATMENTS BASED ON GENOMICS, F.A.C.T. TESTING, AND EVIDENCE OF HEAVY METAL TOXICITY AND MOLD TOXICITY

Instructions to Patients in the Clinical Study

The patients were given the following instructions with respect to the supplement protocol:

- The first two supplement tablets are difficult to break into quarters. We recommend that you obtain (from any pharmacy) a good-quality pill splitter to assist with this process. They can, alternatively, be crushed into powders, then separated on a flat surface, and the powders can be mixed together. They can be taken orally with water, with or without food.

- Occasionally these can make patients sleepy, so some take them at bedtime. They can be taken any time of day, with or without food.

- GO SLOWLY. Occasionally, as the methylation cycle blockages are released, toxins are released and processed by the body, and this can lead to an exacerbation of symptoms. IF THIS HAPPENS, try smaller doses, every other day. SLOWLY work up to the full dosages. If you have questions, please call our office to discuss them.

Results of the Clinical Study

- Various patients reported some early exacerbation of symptoms, which in most cases was followed by a greater improvement in symptoms. Three patients decreased their dosage frequency to every second or third day for several days, until they could tolerate the full daily dosage schedule.

- Sixteen of 30 patients (53%) reported an initial worsening of symptoms, beginning in most of these cases within 3 or 4 days, but in some cases beginning at up to 2 weeks. Most of the symptoms were mild, and none of the patients discontinued usage of the supplements during the first 3 months.

Results of the Clinical Study (continued)

- Most common side effects: gastrointestinal (pain, cramps, constipation, or diarrhea), reported by 6 out of 30 patients or 20%; increase in pain, reported by 4 out of 30 or 13%; and increase in fatigue, reported by 3 out of 30 or 10%. Other symptoms, reported by one patient each, were a decrease in appetite, poor sleep, weak legs, flu-like symptoms, and an increase in anxiety and depression.

- For those who experienced improvement, the time to self-reported improvement on the protocol was an average of 5.6 weeks, with a range from immediate improvement (which was rare) to as long as 8 weeks before improvement was experienced.

Study Results at 3 months

- All 30 patients completed the study requirements at 3 months.
- 25 out of 30 patients reported improvement (83%).
- Among the group that reported improvement, 8 out of 30 reported marked improvement (27%).

DROPOUTS

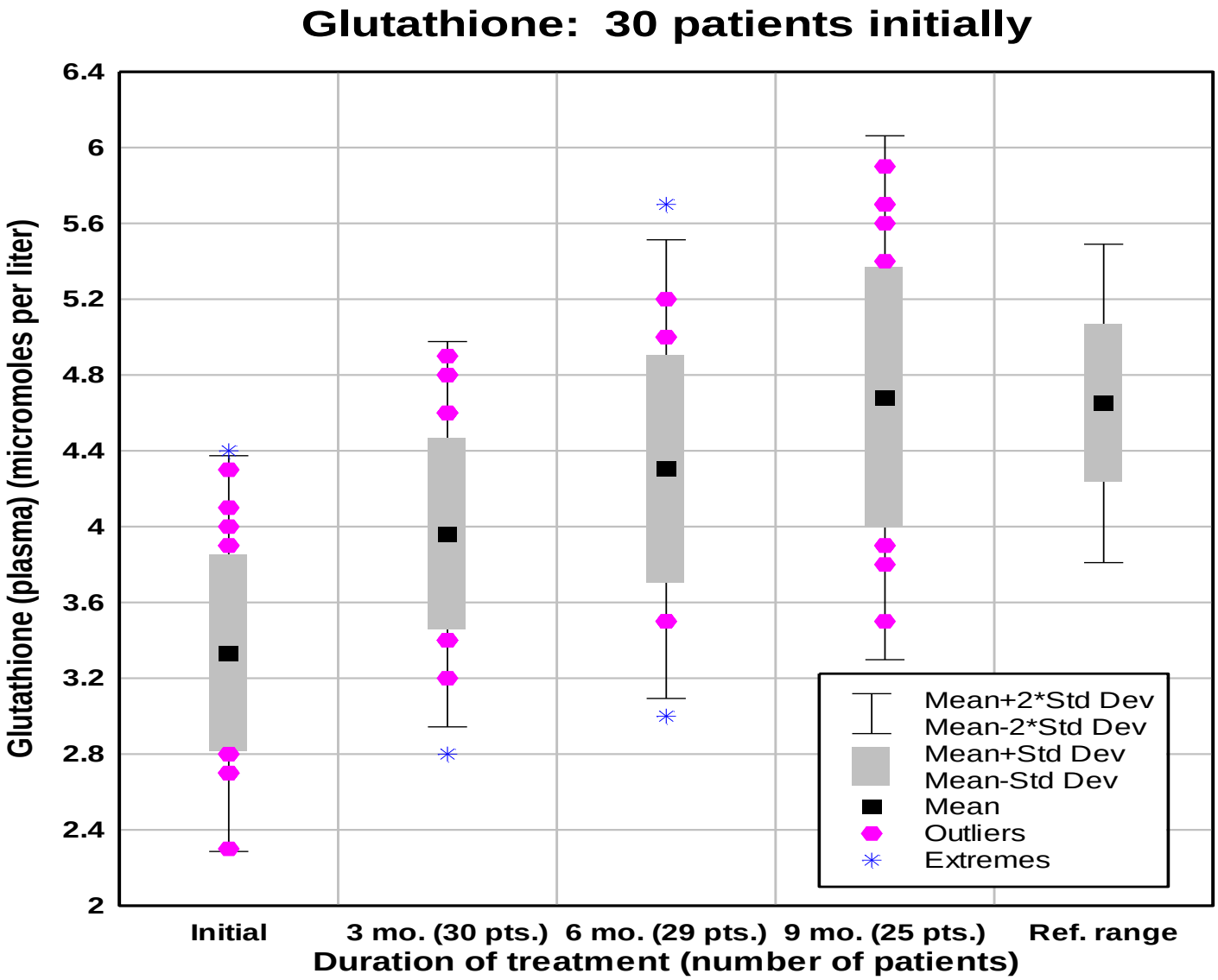
- All 30 patients completed the study at 3 months
- 29/30 patients completed the study at 6 months
- 25/30 patients completed the study at 9 months

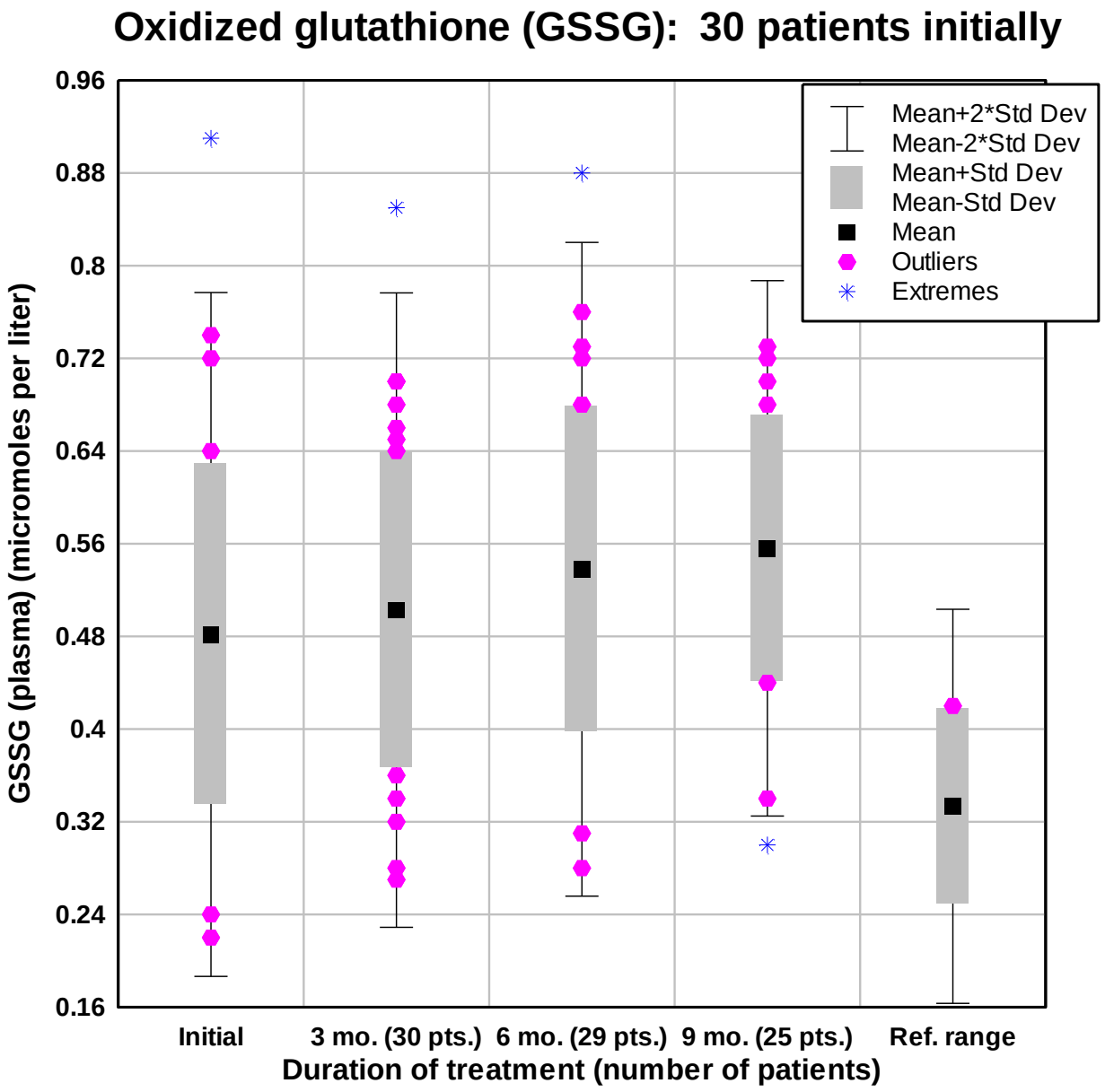
- The patient who dropped out before 6 months reported 100% relief of pain and 60% overall improvement, but her family insisted that she be followed at another clinic.

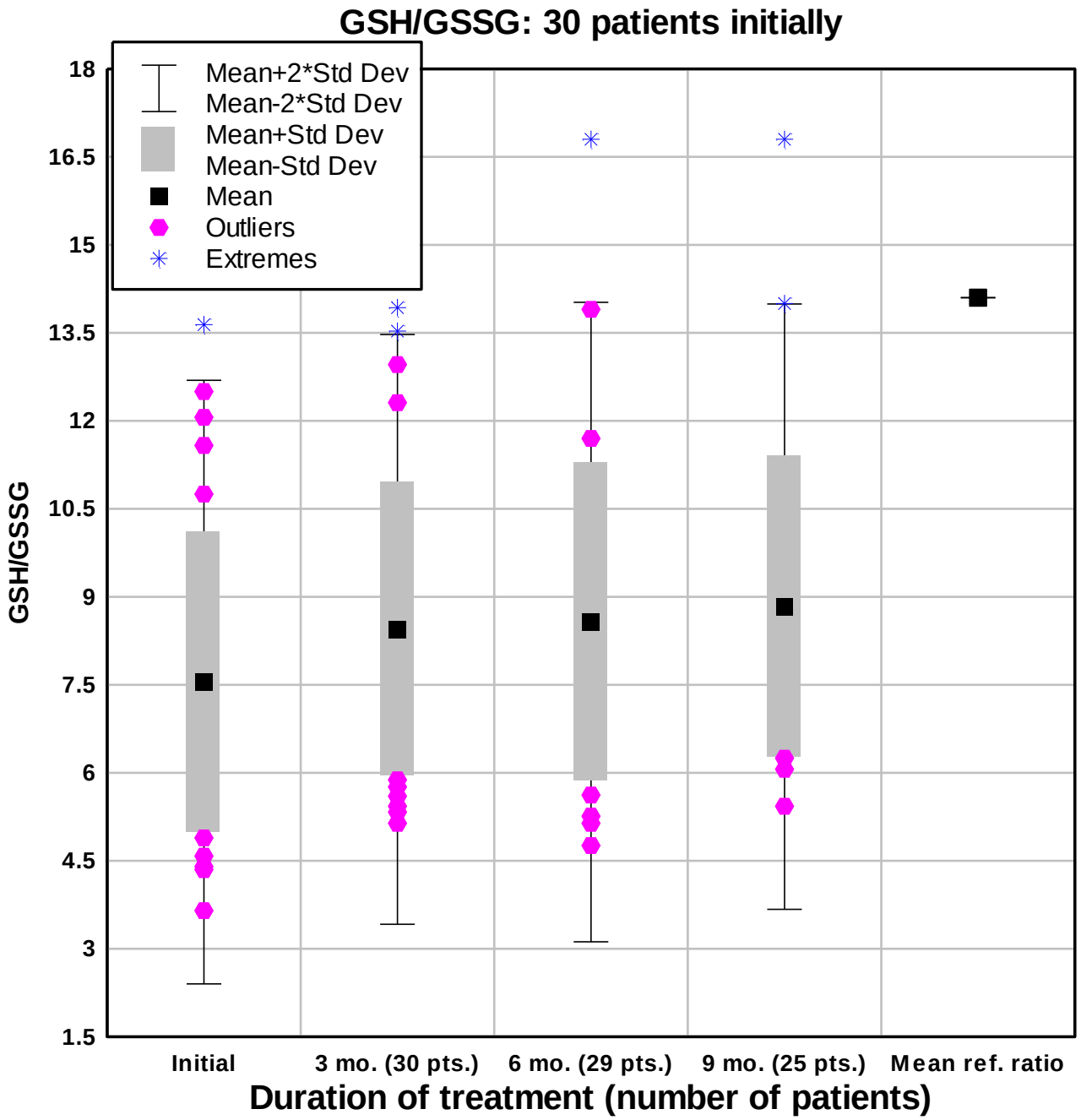
DROPOUTS (continued)

After six months:

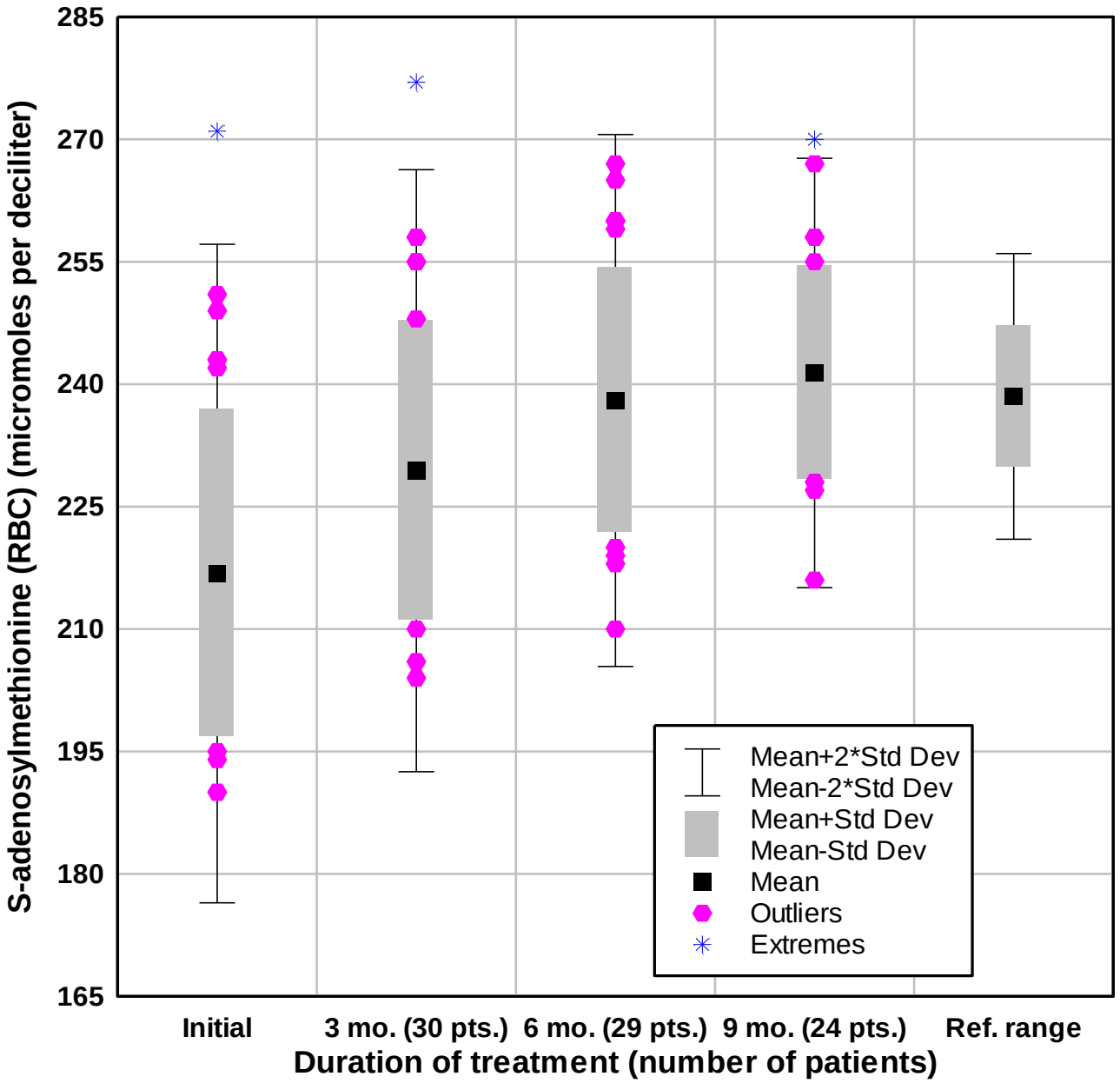
- Two patients reported complete relief of pain, complete relief of symptoms, returned to work at full capacity and decided not to continue the study.
- One patient underwent bilateral hip replacement surgery and could not return for follow up.
- One patient was disappointed with her results and elected to discontinue her treatment.

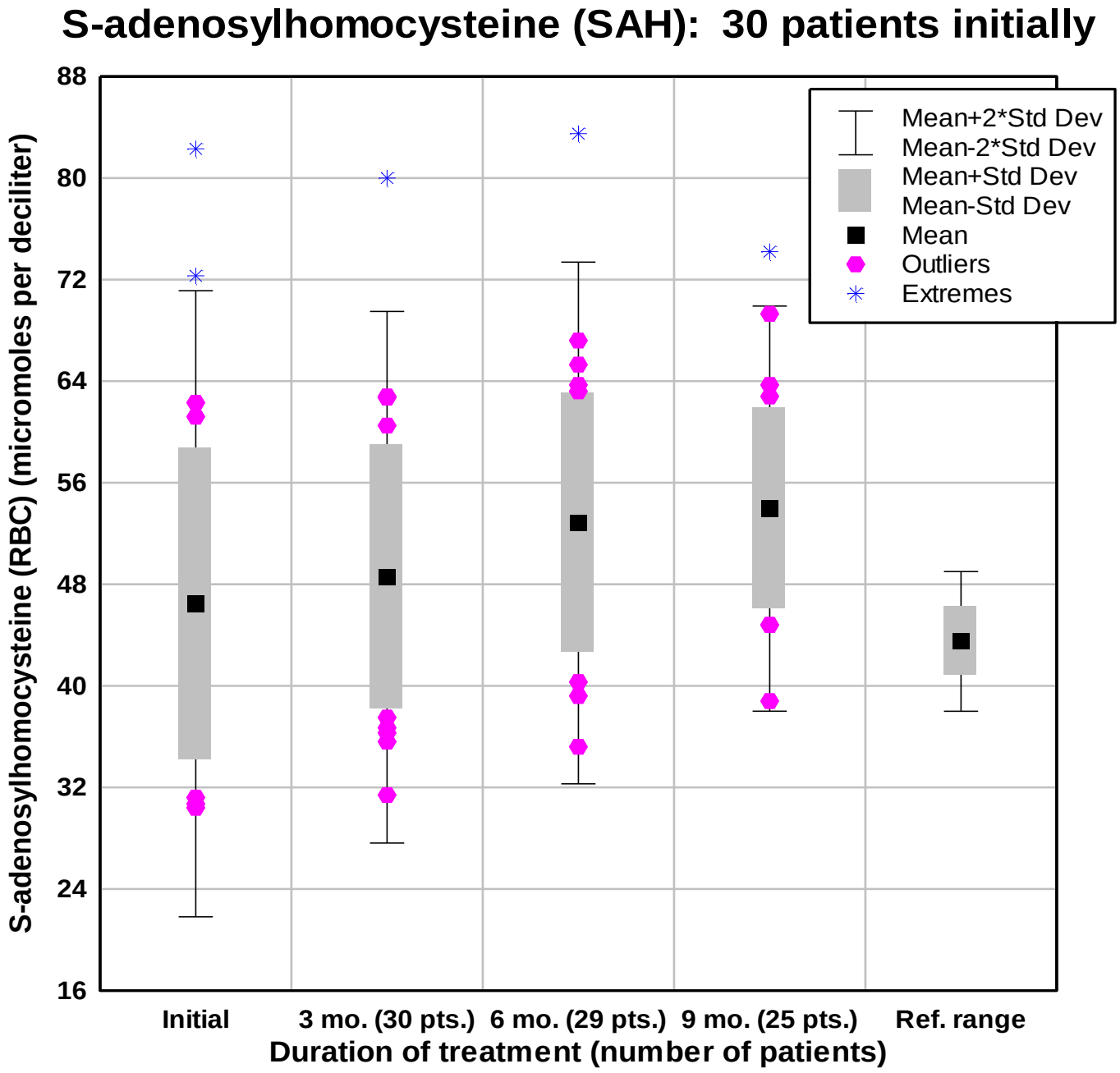

Glutathione: 30 patients initially
Glutathione (plasma) (micromoles per liter)
6.4
6
5.6
5.2
4.8
4.4
4
3.6
3.2
2.8
2.4
2
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Ref. range
Duration of treatment (number of patients)
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes

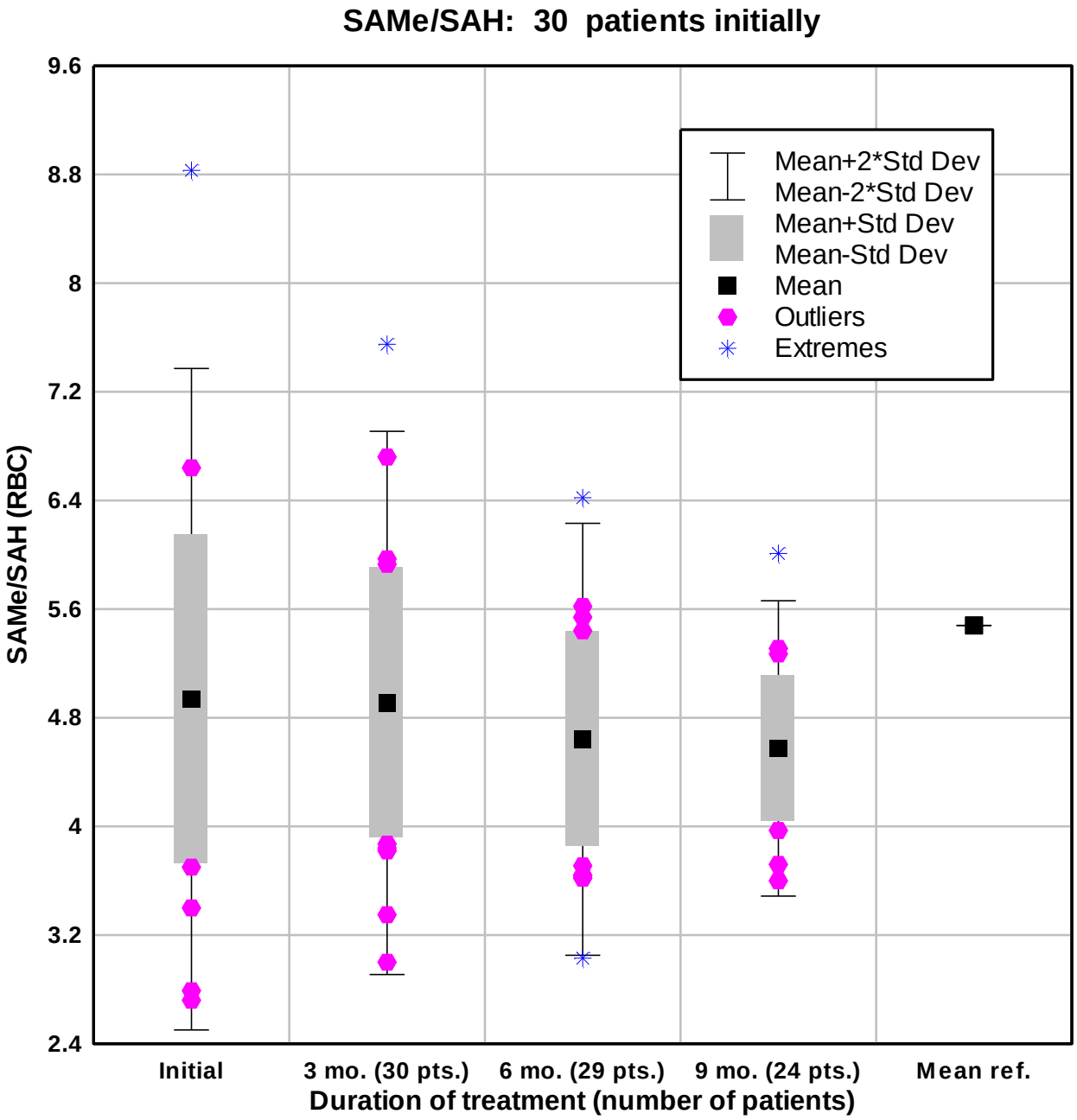

Oxidized glutathione (GSSG): 30 patients initially
GSSG (plasma) (micromoles per liter)
0.96
0.88
0.8
0.72
0.64
0.56
0.48
0.4
0.32
0.24
0.16
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Ref. range
Duration of treatment (number of patients)

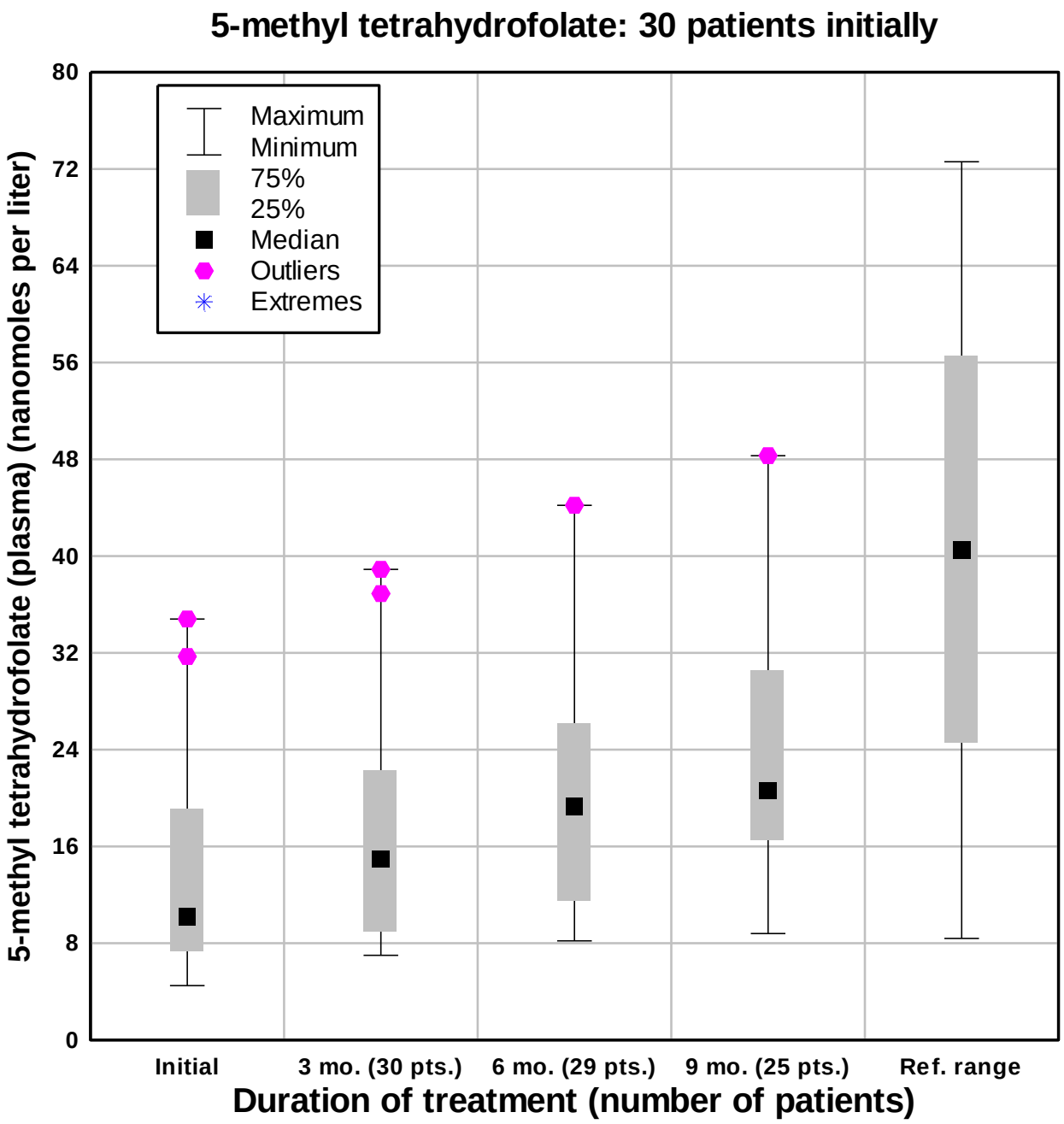

GSH/GSSG: 30 patients initially
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes
18
16.5
15
13.5
12
10.5
9
7.5
6
4.5
3
1.5
GSH/GSSG
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Mean ref. ratio
Duration of treatment (number of patients)

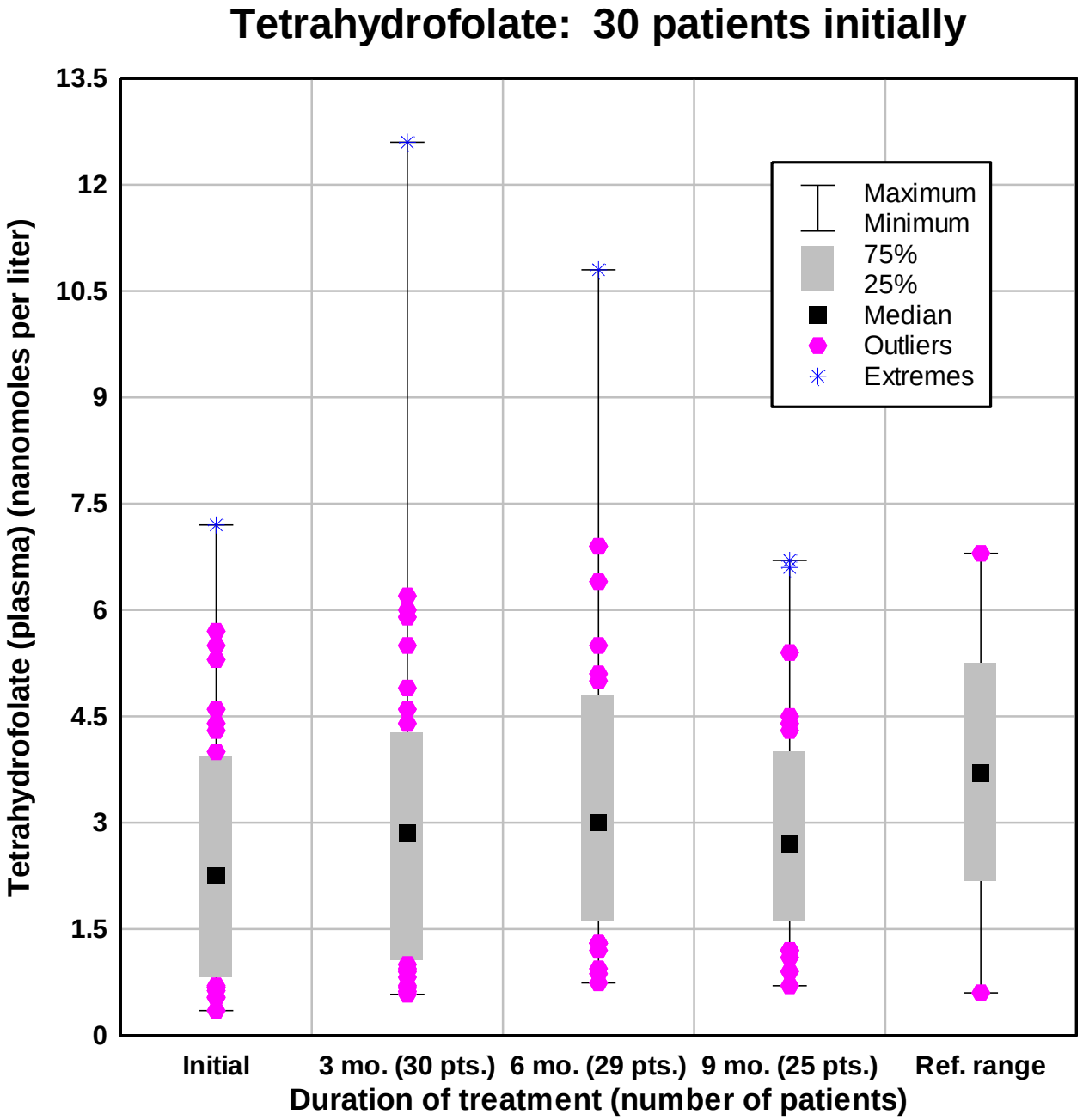
S-adenosylmethionine (SAMe): 30 patients initially

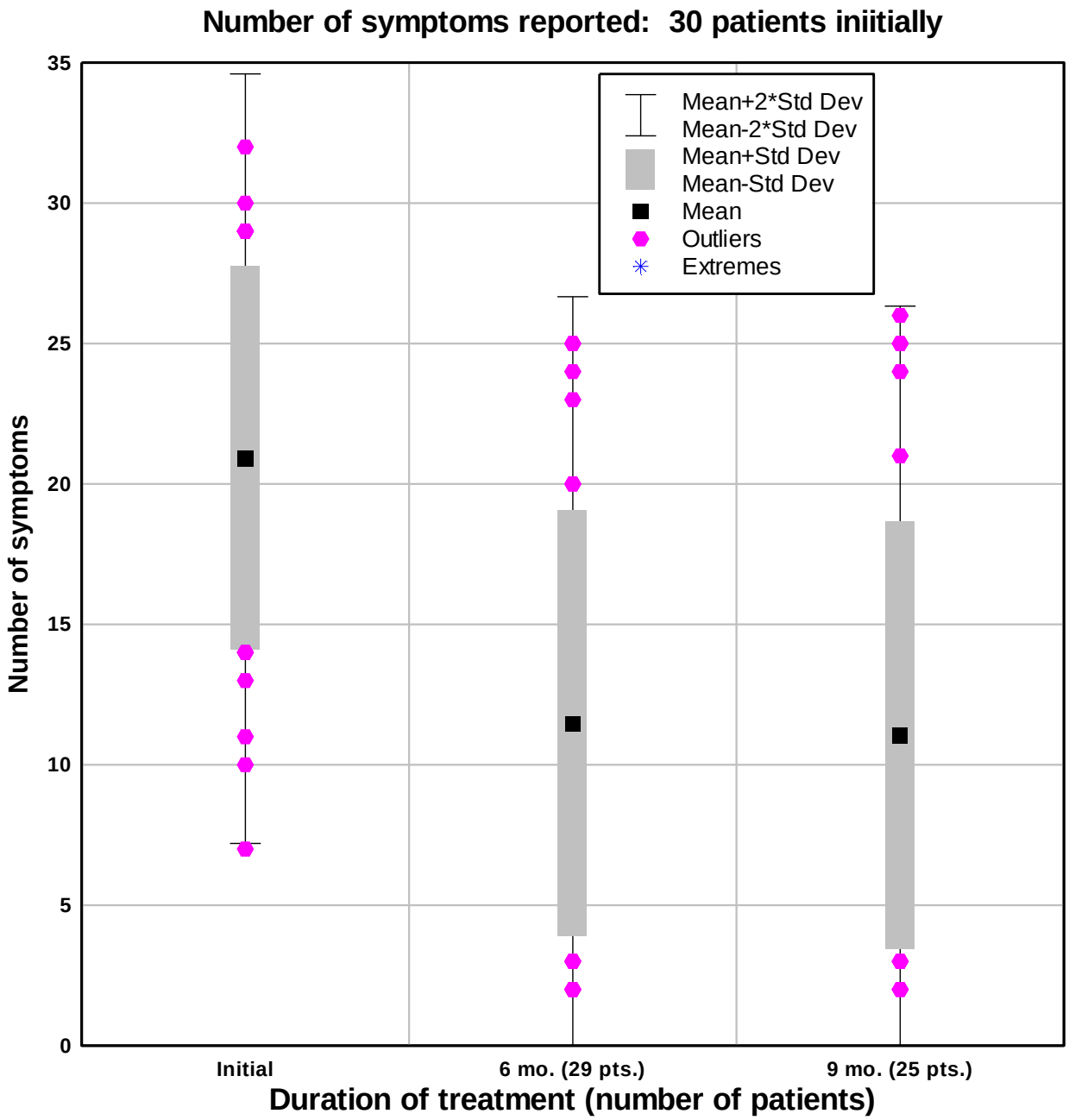


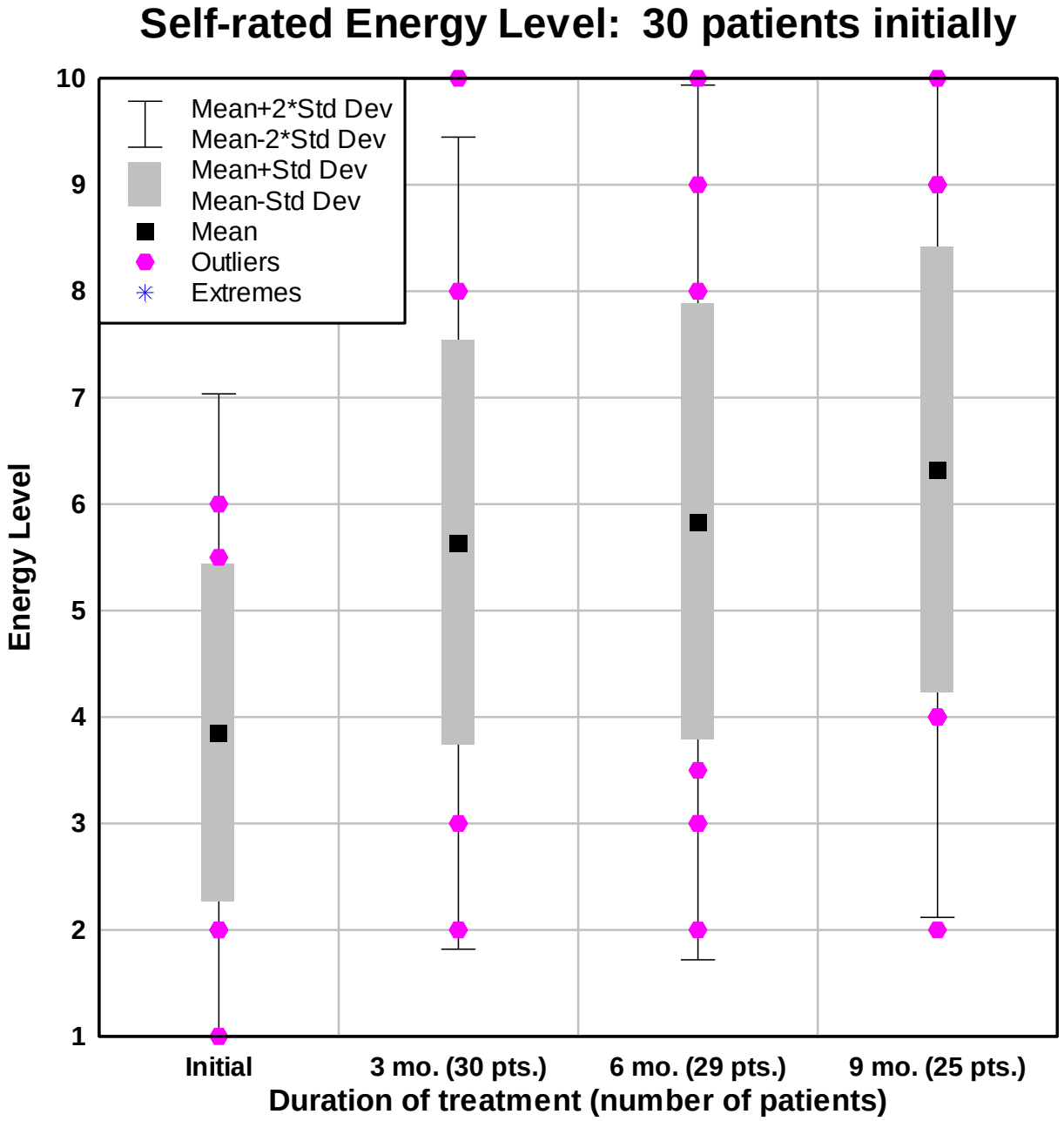

S-adenosylhomocysteine (SAH): 30 patients initially
S-adenosylhomocysteine (RBC) (micromoles per deciliter)
88
80
72
64
56
48
40
32
24
16
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Ref. range
Duration of treatment (number of patients)

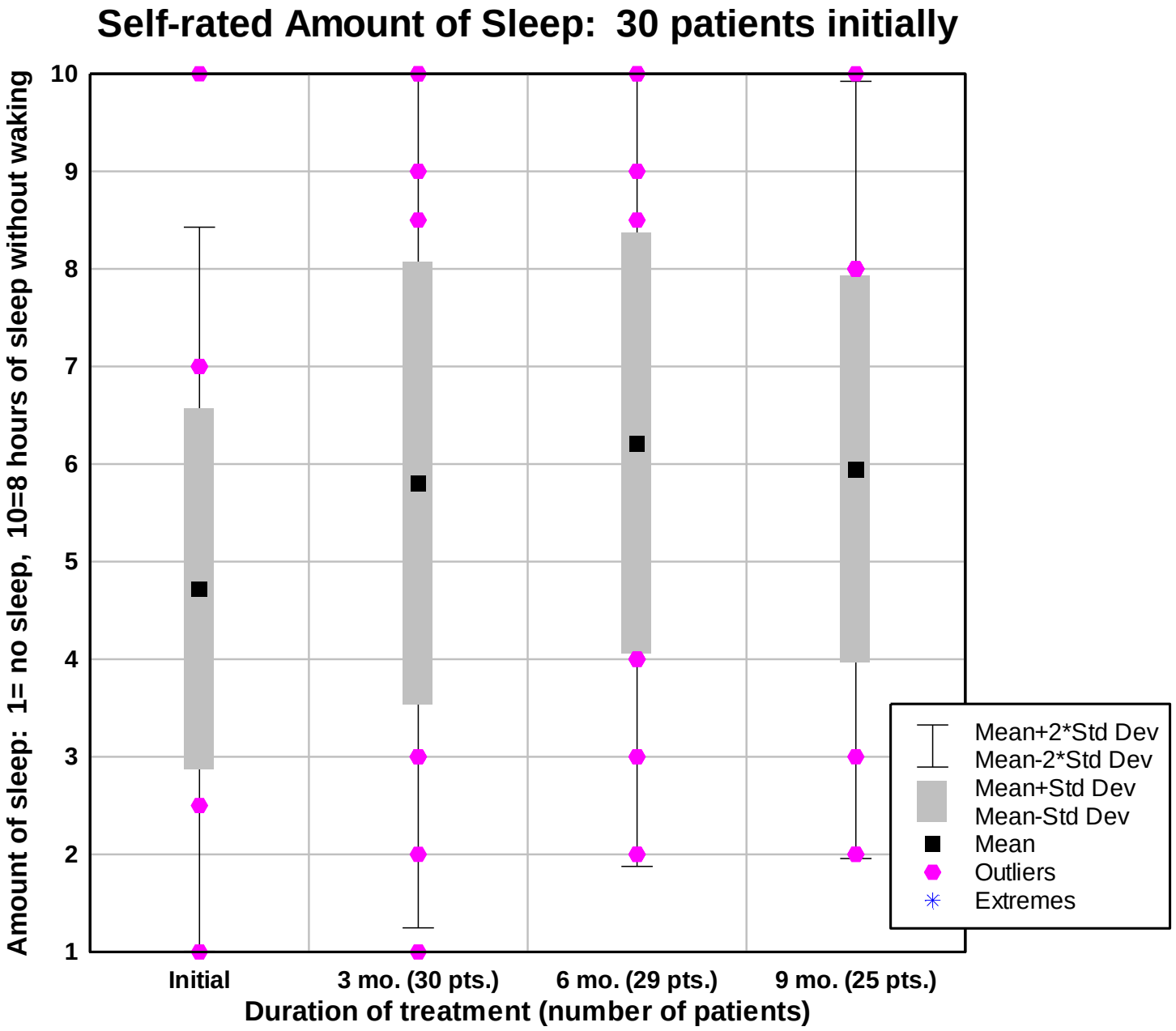

SAMe/SAH: 30 patients initially
9.6
8.8
8
7.2
6.4
5.6
4.8
4
3.2
2.4
SAMe/SAH (RBC)
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (24 pts.)
Mean ref.
Duration of treatment (number of patients)

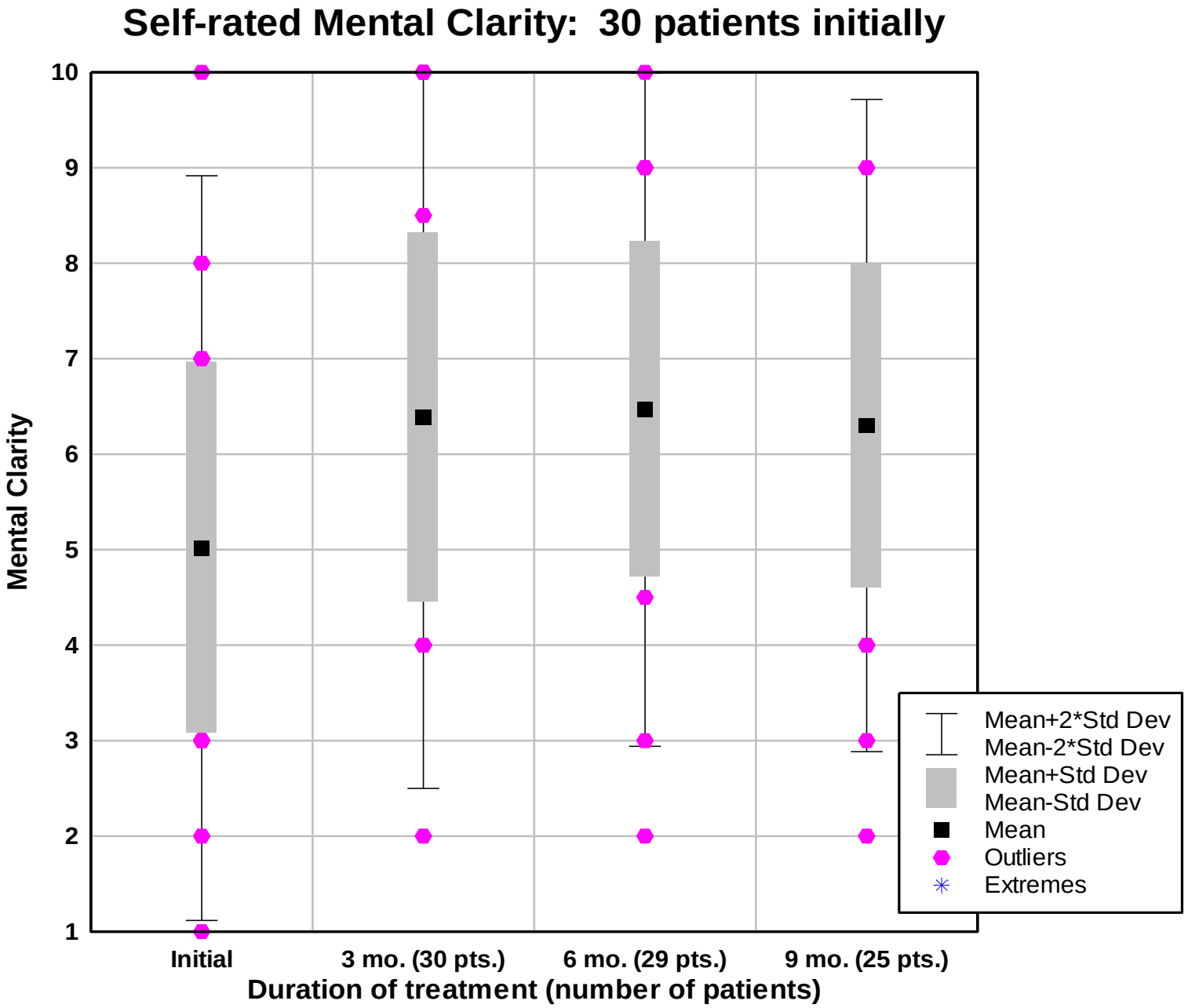

5-methyl tetrahydrofolate: 30 patients initially
Maximum
Minimum
75%
25%
Median
Outliers
Extremes
5-methyl tetrahydrofolate (plasma) (nanomoles per liter)
80
72
64
56
48
40
32
24
16
8
0
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Ref. range
Duration of treatment (number of patients)

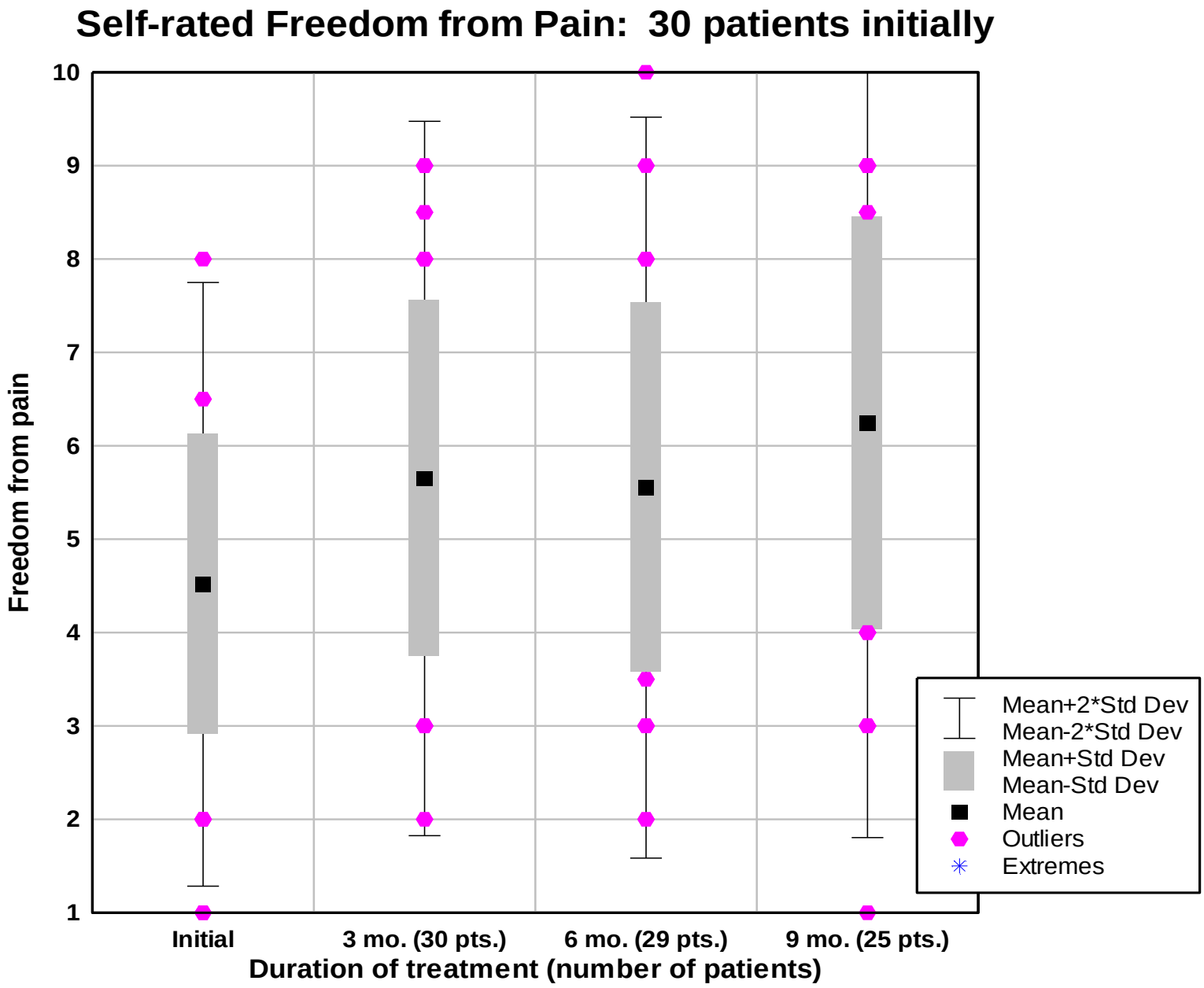

Tetrahydrofolate: 30 patients initially
Tetrahydrofolate (plasma) (nanomoles per liter)
13.5
12
10.5
9
7.5
6
4.5
3
1.5
0
Maximum
Minimum
75%
25%
Median
Outliers
Extremes
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Ref. range
Duration of treatment (number of patients)

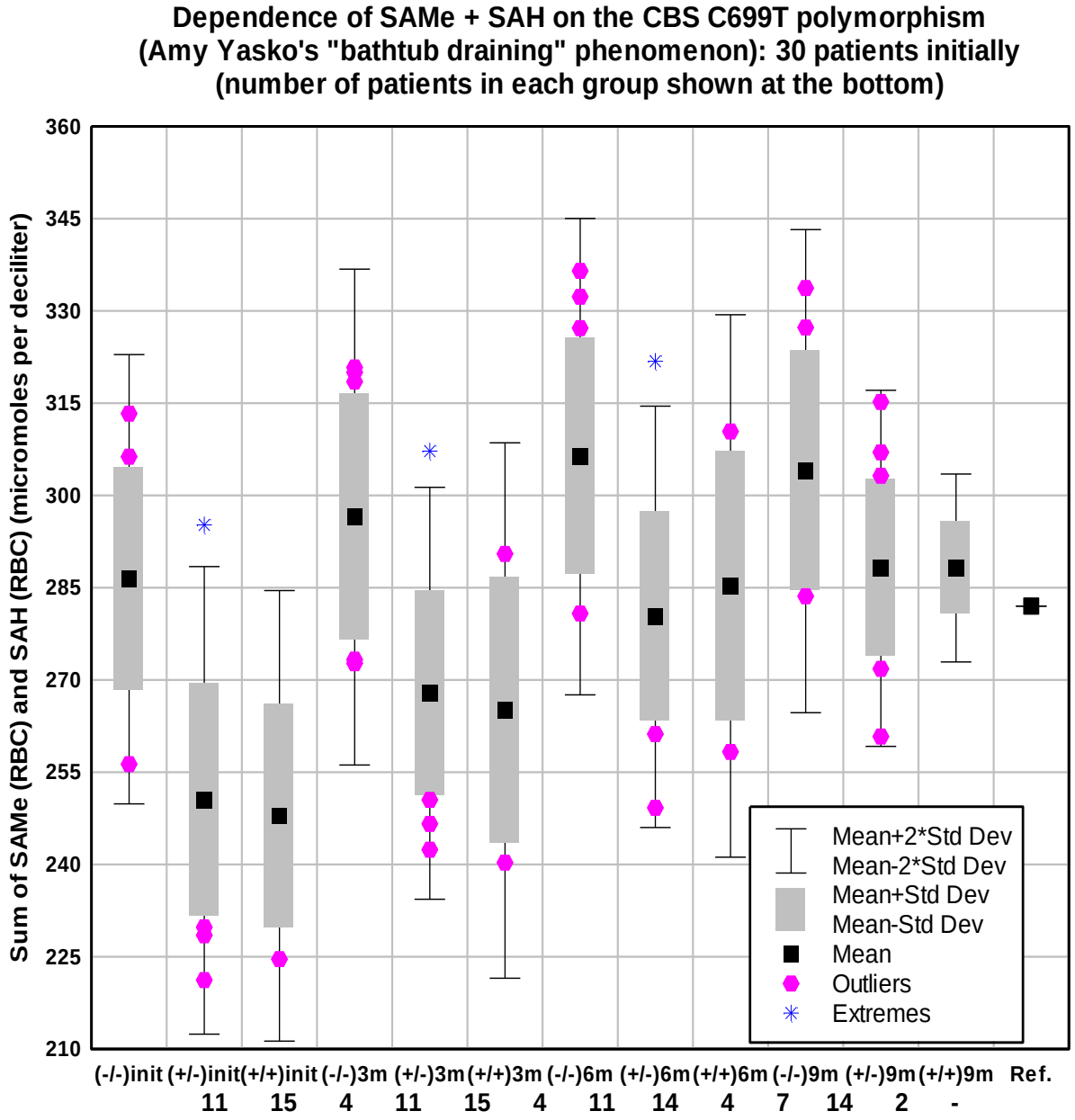

Number of symptoms reported: 30 patients iniitially
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes
35
30
25
20
15
10
5
0
Number of symptoms
Initial
6 mo. (29 pts.)
9 mo. (25 pts.)
Duration of treatment (number of patients)


Self-rated Energy Level: 30 patients initially
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes
Energy Level
10
9
8
7
6
5
4
3
2
1
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Duration of treatment (number of patients)


Self-rated Amount of Sleep: 30 patients initially
Amount of sleep: 1= no sleep, 10=8 hours of sleep without waking
10
9
8
7
6
5
4
3
2
1
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Duration of treatment (number of patients)
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes


Self-rated Mental Clarity: 30 patients initially
Mental Clarity
10
9
8
7
6
5
4
3
2
1
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Duration of treatment (number of patients)
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes


Self-rated Freedom from Pain: 30 patients initially
Freedom from pain
10
9
8
7
6
5
4
3
2
1
Initial
3 mo. (30 pts.)
6 mo. (29 pts.)
9 mo. (25 pts.)
Duration of treatment (number of patients)
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes


Dependence of SAMe + SAH on the CBS C699T polymorphism
(Amy Yasko's "bathtub draining" phenomenon): 30 patients initially
(number of patients in each group shown at the bottom)
Sum of SAMe (RBC) and SAH (RBC) (micromoles per deciliter)
360
345
330
315
300
285
270
255
240
225
210
(-/-)init
(+/-)init
(+/+)init
(-/-)3m
(+/-)3m
(+/+)3m
(-/-)6m
(+/-)6m
(+/+)6m
(-/-)9m
(+/-)9m
(+/+)9m
Ref.
11
15
4
11
15
4
11
14
4
7
14
2
-
Mean+2*Std Dev
Mean-2*Std Dev
Mean+Std Dev
Mean-Std Dev
Mean
Outliers
Extremes

Outcomes after 9 months

- At 9 months, 15 of the 25 patients remaining in the study at that time reported that they had experienced >50% improvement.
- Three of the 5 patients who had dropped out had also reported >50% improvement.
- Adding these together, 18 out of the original 30 patients (or 60% of them) reported >50% improvement.

CASE STUDY #1

- D.F. was a 49 yo wf with a 6 year hx of FM and CFS. Her initial glutathione 3.0 (nl 3.8-5.5) and SAM 217 (nl 221-256). Although she felt a little better after the first 3 months of supplements, glutathione was 2.8, SAM 226 on f/u. (CBS +) After 6 months, GSH 3.5 and SAM 240. Still minimal clinical improvement. After beginning NH3 RNA, Nucleotides and Trehalose (24 hr urine aa showed elevated taurine and cysteine) at 6 months…

CASE STUDY #1

After just one month on those supplements, she felt so much better that she was able to resume full time work, which she had not been able to do for 5 years, successfully. She was free of pain and her energy was back to normal. 9 month levels of GSH were 4.0 and SAM 240.

CASE STUDY #2

- B.E. was an 84 yo wf with a two year history of FM and CFS. Her initial GSH was 2.7, SAM was 201. She reported no clinical improvement at 3 months, but had two episodes of severe infection requiring two rounds of antibiotics during that time. Her GSH was 3.2 and SAM 220 at 3 months. At 6 months, still no improvement and GSH only 3.0, SAM 233. Since she had a +FACT she was evaluated

CASE STUDY #2

- for heavy metal toxicity with DMPS challenge test (elevated levels of mercury were found) and treated with cholestyramine for mold exposure, and DMPS IV monthly with oral DMSA. By the completion of the study, she reported marked improvement, and was able to join her friends for a week-long visit to Paris, noting she was pain free and her energy had returned to almost normal. At 9 months, GSH 4.0 and SAM 232.

CASE STUDY #3

- S.H. was a 55 yo wf with FM and CFS for 8 years. She was on disability for those conditions. We had discovered an elevated level of mercury on DMPS testing 4 years prior (level: 34) but she elected not to treat it for financial reasons. Initial GSH level was 3.4, SAM 207. These rose over the study period: GSH at 3 months 3.9, and 6 months 4.8 and at 9 months 4.6.

CASE STUDY #3

- SAM rose to 219 at 3 months, 230 at 6 months and 267 at 9 months. While noting a 20% improvement in energy, sleep and well-being, no additional improvements were noted. She continued to decline to treat the elevated mercury level.

AFTER 9 MONTHS OF STUDY: One Additional Component

- 9 of our 25 remaining patients still had significantly elevated adenosine levels.
- All agreed to a 2-3 month trial of acyclovir
- Dosage of acyclovir: 200mg 5x a day
- Results: 8 of 9 patients reported an additional 20% improvement in overall well-being, which held even when acyclovir was discontinued.

Are the 9-month results of this study consistent with the predictions of the Glutathione Depletion—Methylation Cycle Block hypothesis?

Yes, as follows:

1. The reduced glutathione levels were significantly below normal before treatment was begun.

2. There was a partial methylation cycle block before treatment was begun.

3. The methylation cycle block was partially lifted by treating with bioactive forms of vitamin B12 and folate, together with basic nutritional support, directed specifically at raising the activity of the enzyme methionine synthase, which is the enzyme hypothesized to be partially blocked.

Are the 9-month results of this study consistent with the predictions of the Glutathione Depletion—Methylation Cycle Block hypothesis? (continued)

4. Treating to lift the methylation cycle block not only improved the methylation capacity, but also raised glutathione (as well as the ratio of reduced to oxidized glutathione), suggesting that these two phenomena are indeed linked in an interactive mechanism in CFS, as they also appear to be in autism.

5. The mean level of reduced glutathione rose by 47%, while the mean level of oxidized glutathione rose less than 5%, suggesting that the main issue involving glutathione in CFS is a deficit in production, rather than a deficit in recycling. (However, it must be noted that B2 and B3 supplements were included in the protocol, which may have increased the activity of glutathione reductase to some extent.)

What lab tests can be used to see if the GD-MCB hypothesis applies to a given case of CFS?

- The methylation pathways panel (offered by Health Diagnostics and Research Institute (formerly Vitamin Diagnostics, Inc.) is the most definitive for detecting methylation cycle block and glutathione depletion.

- Urine organic acids testing for methylmalonic acid and formiminoglutamic acid (“figlu”) are also very helpful. When these are elevated, they indicate low adenosylcobalamin and low tetrahydrofolate, respectively. When both methylamalonic acid and figlu are elevated, it is very likely that methionine synthase is partially blocked.

The Bottom Line

- A hypothesis has been developed to explain chronic fatigue syndrome (CFS).
- Key features: a chronic partial block of the methylation cycle, significant draining of folate from the cells, and a chronic depletion of glutathione.
- Explains: genetic predisposition, biochemical abnormalities, and many seemingly unconnected symptoms of CFS.
- Tested in a clinical study using a simplified treatment extracted from the full treatment program of Dr. Amy Yasko, and results are found to be consistent with the hypothesis.
- Lab testing is available to determine whether the hypothesis applies to a particular patient. So far it appears to apply to most CFS patients.
- This simplified Yasko treatment is currently producing significant benefits in most patients who use it, and it has resulted in apparently complete recovery in a small number of patients. Additional benefit can be obtained by incorporating additional parts of the complete Yasko protocol.

Acknowledgments

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- Management was provided by Kevin Joyce, and nursing support was provided by Neva Dix. We are very grateful to them as well.

- Finally, we extend special thanks to the patients who were willing to participate in this study.

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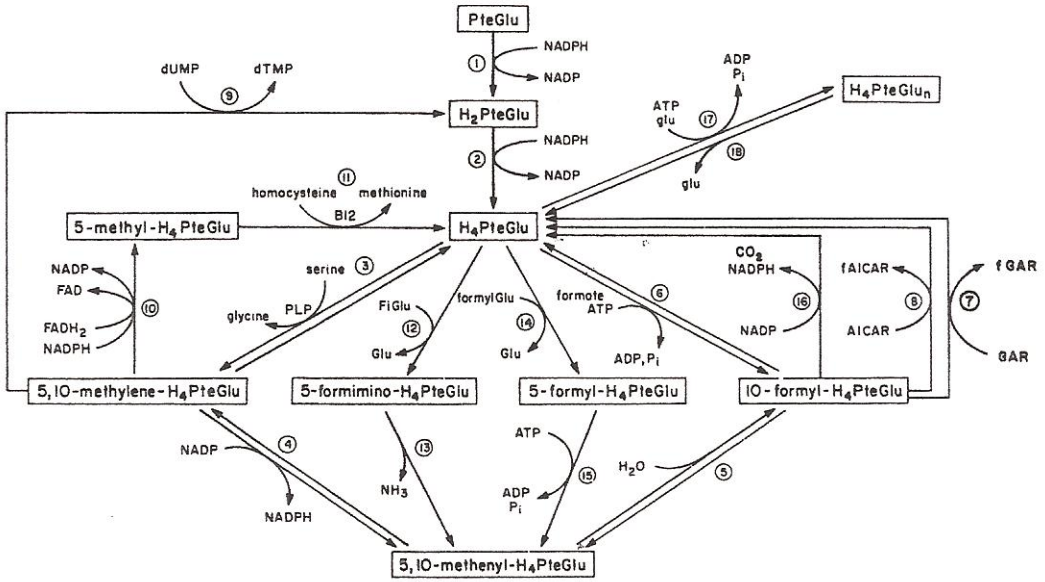
  Dr. Nathan's new book "On Hope and Healing: For Those Who Have Fallen through the Medical Cracks" is available from Gordon Medical Associates: info@gordonmedical.com

Brody and Shane



Genetic polymorphisms (SNPs) associated with CFS

- **So far, SNPs in genes for the following proteins have been found to be present at higher frequency in CFS in general or in a subset, either alone or in combination:**

  Immune system:

  - **Tumor necrosis factor (TNF)**
  - **Interferon gamma (IFN-gamma)**

  Neurotransmitter systems:

  - **Tryptophan hydroxylase 2 (TPH2)**
  - **Serotonin transporter (5-HTT) gene promoter**
  - **Serotonin receptor subtype HTR2A**
  - **Monoamine oxidase A (MAO A)**
  - **Monoamine oxidase B (MAO B)**
  - **Catechol-O-methyltransferase (COMT)**

  HPA Axis:

  - **Angiotensin converting enzyme (ACE)**
  - **Proopiomelanocortin (POMC)**
  - **Corticosteroid binding globulin (CBG)**
  - **Glucocorticoid receptor--nuclear receptor subfamily3, group C, member 1 (NR3C1)**

  All of these proteins play roles in the pathogenesis described by this hypothesis.