



The Metagenics
**Healthcare Institute
for Clinical Nutrition**

Specialized Pro-resolving Mediators in real world clinical practice

GRAND ROUNDS

Jennifer Stagg, ND
Avon, CT

Chronic Inflammation leads to many chronic diseases



Inactivity



Obesity



Aging



Chronic Systemic Inflammation



Adipocytes



Insulin Resistance,
Type 2 Diabetes



Immune Cells



Atherosclerosis



Brain Cells



Alzheimer's,
Huntington's,
Parkinson's



Systemic and local increase in cytokine concentrations



Cancer



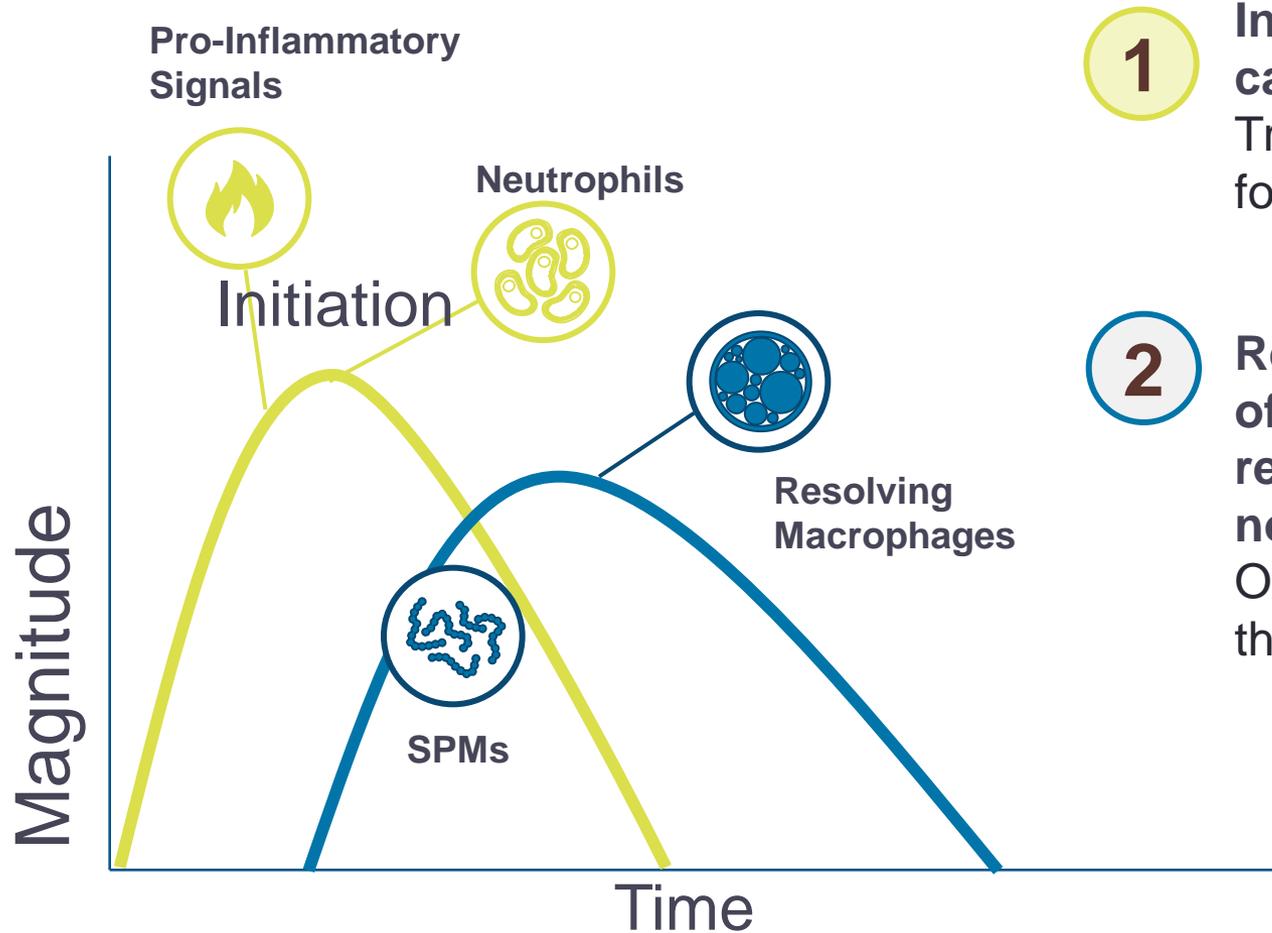
Immune Cells



Arthritis

Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature*. 2008 24;454(7203):463-9.

Multi-step process of acute inflammation and resolution



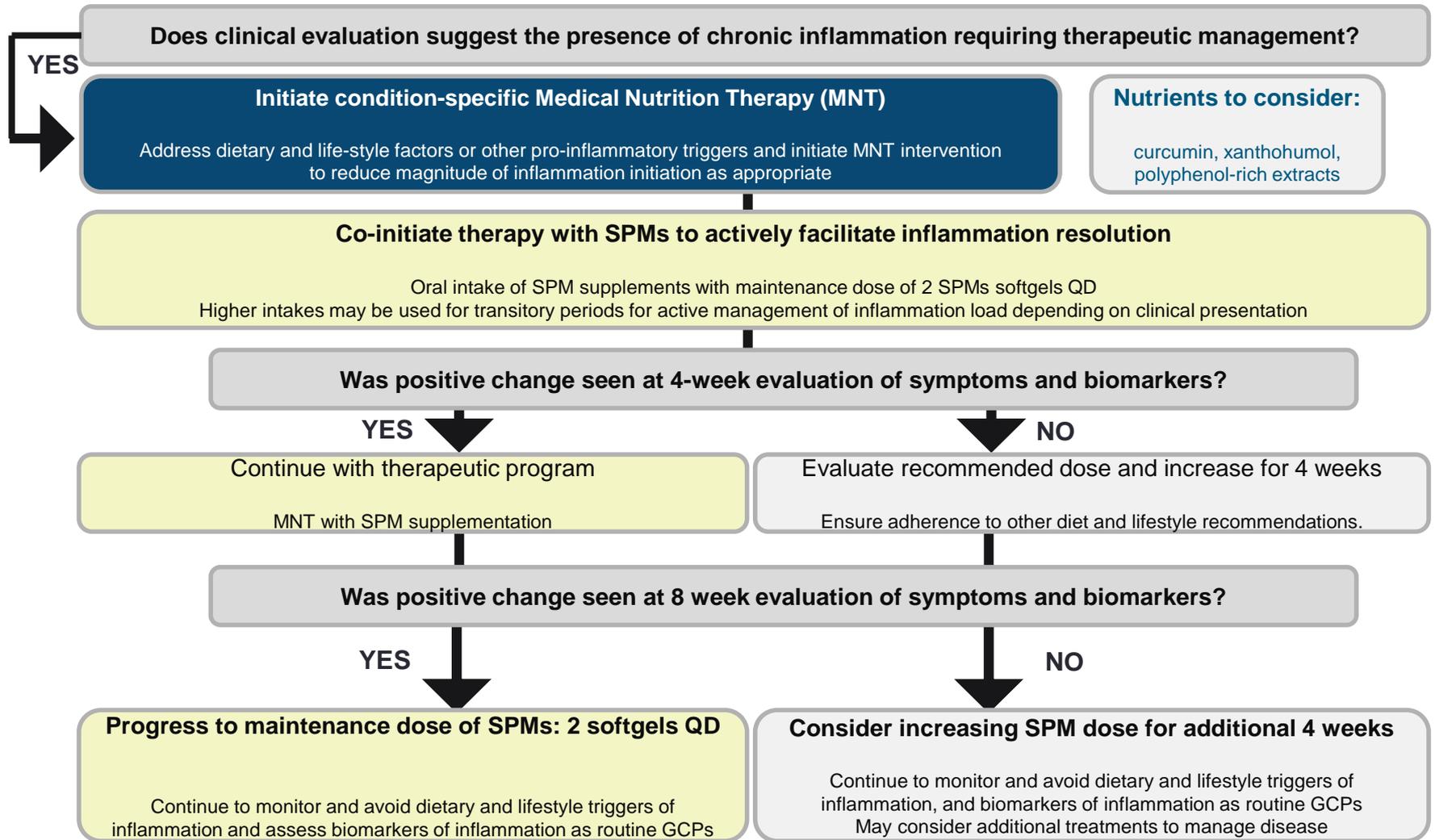
1 Initiation – eradicate cause of inflammation. Treatment has been focused.

2 Resolution – subsidence of inflammation and restoration to previous normal condition. Opportunity for novel therapy.

Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. 2014;510(7503):92-101.

Spite M, Clària J, Serhan CN. Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. *Cell Metab*. 2014;19(1):21-36.

Algorithm to incorporate SPMs in patients with chronic inflammation



Recommended patient assessment tools to evaluate initial presentation and track progress

Clinically measureable biomarkers of inflammation including:

- hsCRP
- TNF-alpha
- Ferritin
- ESR
- Fibrinogen

Condition-specific questionnaires and quality of life forms including:

- Brief Pain Inventory
- American Chronic Pain Association Quality of Life Scale
- SF-12

Symptomatic measurement scales:

- MSQ/HSQ

Case #1

50 year old Caucasian woman: Trainer

Case #1: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Week 4 follow-
up

History & Complaints:

- Middle aged woman with history of mild to moderate migraines and anxiety
- Main complaints of bilateral pain in shoulders and arms for the past 6 mos
 - Pain sometimes extends to both hands with throbbing aches
 - Pain not relieved with heat or cold
 - 7/10 Severity

Tot

On Examination:

- Height: 5'3"
- Weight: 147lbs
- BMI: 25.23kg/m²
- BP: 115/78 mm Hg
- Pulse: 66/min, reg
- Temp: 98.7 (F)

Case #1: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Current therapy:

- Topiramate (QD) for migraines
- Venlafaxine (QD) for anxiety
- Fiber supplement (QD)
- Multi-vitamin supplement (QD)
- Vitamin D supplement (QD)

Past Medical History:

- Mild to moderate migraines
- Mild anxiety
- Fibromyalgia

Relevant Family History:

- None

Case #1: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

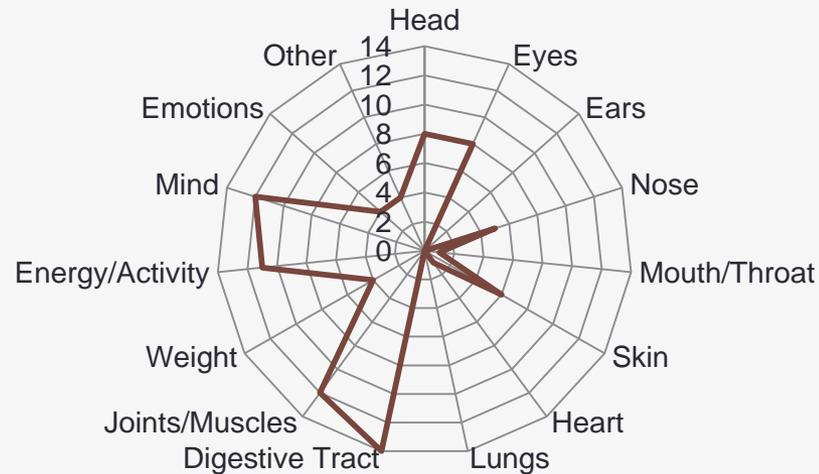
Labs & Tests

(normal range)

Visit 1

hsCRP (0 – 3 mg/l)	0.19
Ferritin (15 – 150 ng/dl)	18
Fibrinogen (199 – 504 mg/dl)	267
ESR (0 – 32 mm/Hr)	2
IL-6 (0-15.3 pg/ml)	0.97
BNP (0 – 100 pg/ml)	9
Omega-3 index (>/=5.5 %by weight)	3.9

MSQ Total score = 90



Case #1: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
7	2	5	6

Scale:

- 1 – no pain
- 10 – pain as bad as you can imagine

Brief Pain Inventory

In past 24-hours how much has pain interfered in your:

- Scale from 1 (does not interfere) to 10 (completely interferes)

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
5	5	3	6	1	7	7

American Chronic Pain Association Quality of Life Scale

6

- Work/volunteer limited hours
- Take part in limited social activities on weekends

Case #1: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Management plan:
integration of SPMs into ongoing patient care

Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests



- Add 6 SPM softgels/day for 4 weeks
- Continued with existing medications

Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests

Case #1: Week 4 follow up visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Presentation:

- Patient reports improvement overall and especially during the 4th week
 - wakes up w/o pain
 - rates pain as 1/10 severity and in L shoulder
 - Still fatigued and doesn't sleep well

Current therapy:

- SPMs 6 soft gels/day
- Continued with ongoing medications
 - Topiramate (QD)
 - Venlafaxine (QD)
 - Fiber supplement (QD)
 - Multi-vitamin supplement (QD)
 - Vitamin D supplement (QD)

On Examination:

- Temp: 98.8 F; BP: 124/95 mm Hg; P: 80/min, reg
- Weight: 147 lbs ; BMI: 25.23 kg/m²

Management plan:

- Increase SPMs to 8 soft gels/day for ~4 weeks
 - Taper to maintenance dose ~2 soft gels/day once clinical targets are met
- Continue to watch for and avoid dietary and environmental triggers of inflammation
 - obesity, body composition, glucose control, dietary sources, leaky gut, allergy, infection
 - Utilize pharmaceutical anti-inflammatory strategies as needed

Tot

Case #1:4 week follow up

Profile history & examination

Past medical & drug history

Initial labs and tests

Management plan

Week 4 follow-up

Labs & Tests

Visit 2

(normal range)

hsCRP
(0 – 3 mg/l) 1.7 (WNL)

Ferritin
(15 – 150 ng/dl) 22 (WNL)

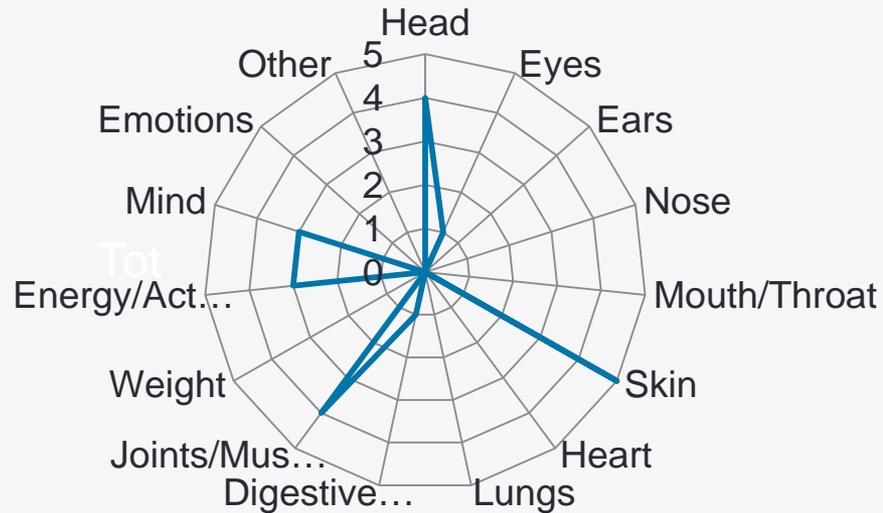
Fibrinogen
(199 – 504 mg/dl) 252 (WNL)

ESR
(0 – 32 mm/Hr) <4.0 (WNL)

BNP
(0 – 100 pg/ml) 31.9 (WNL)

Omega-3 index
(>/=5.5 %by wght) 8.3%

MSQ Total score = 21



Case #1: 4 week follow up visit

Profile history & examination

Past medical & drug history

Initial labs and tests

Management plan

Week 4 follow-up

Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
1 (7 prior)	0 (2 prior)	5 (5 prior)	1 (6 prior)

Scale:

- 1 – no pain
10 – pain as bad as you can imagine

Brief Pain Inventory

In past 24-hours how much has pain interfered in your:

- Scale from 1 (does not interfere) to 10 (completely interferes)

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
0 (5 prior)	0 (5 prior)	0 (3 prior)	0 (6 prior)	0 (1 prior)	1 (7 prior)	0 (7 prior)

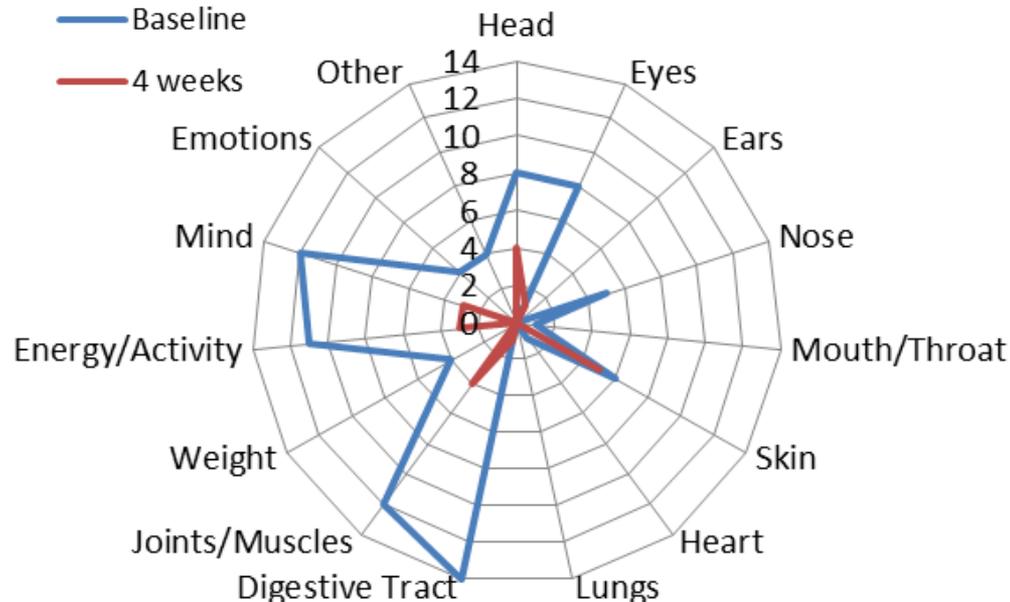
American Chronic Pain Association Quality of Life Scale

10 (6 prior)

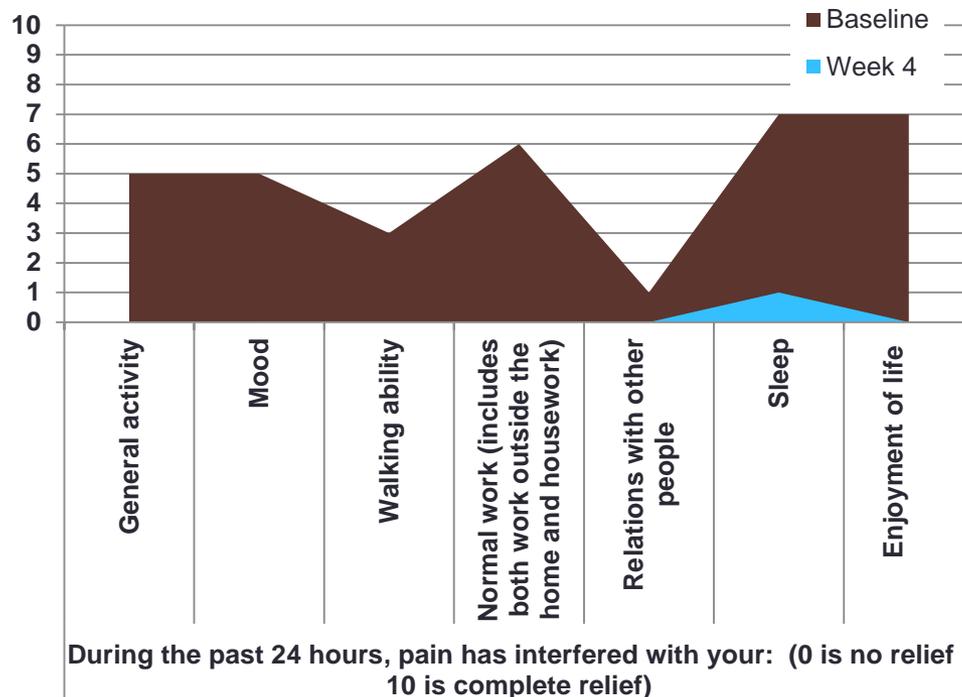
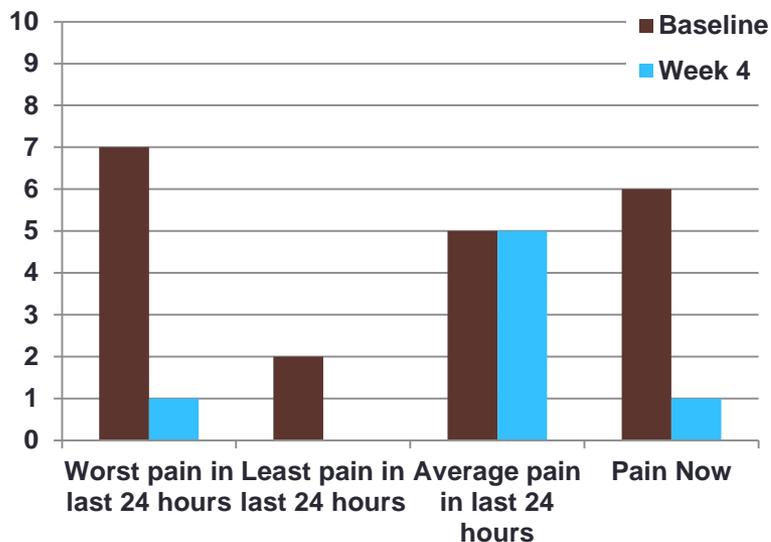
- Go to work/volunteer each day
- Normal daily activities each day
- Have a social life outside of work
- Take an active part in family life

Case #1: Progress summary at 4 weeks

- Plasma inflammatory markers remained within normal limits
 - From baseline visit and again on 4 week follow up
- Functional improvement evident by patient perception and on examination
 - Patient reports feeling less pain and greater mobility
 - Reduced dosages of other analgesics
 - Increased range of motion on physical examination
- Reduction in MSQ (90 to 21)



Case #1: Summary of findings from baseline vs 4 week follow up



American Chronic Pain Association – Quality of Life Scale

Baseline

Score = 6

- Work/volunteer limited hours
- Take part in limited social activities on weekends

4 weeks

Score = 10

- Go to work/volunteer each day
- Normal daily activities each day
- Have a social life outside of work
- Take an active part in family life

Case #2

56 year old Caucasian woman: IT Project Manager

Case #2: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

History & Complaints:

- Perimenopausal female, insulin resistant
- Diagnosed with metabolic syndrome
- Gained 50 lbs over past 6 years
 - About 10 lbs in past year
 - Now considered obese by BMI
 - Diet and exercise regimens are not working
- Main complaint of low back pain
 - 30 years duration with decreased range of motion (ROM)

On Examination:

- Height: 65"
- Weight: 189lbs
- BMI: 31.45kg/m²
- BP: 120/84 mm Hg
- Pulse: 66/min regular
- Temp: 97.5 (F)

Case #2: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Past Medical History:

- Laminectomy 2001
- Foot surgery 2009
For pain management

Relevant Family History:

- None

Current therapy:

- Fish Oil (1200mg QD)
- Vitamin D3 (5000IU QD)
- Multi-vitamin (1 tablet QD)
- Fiber Supplement (1 tablet QD)

Case #2: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

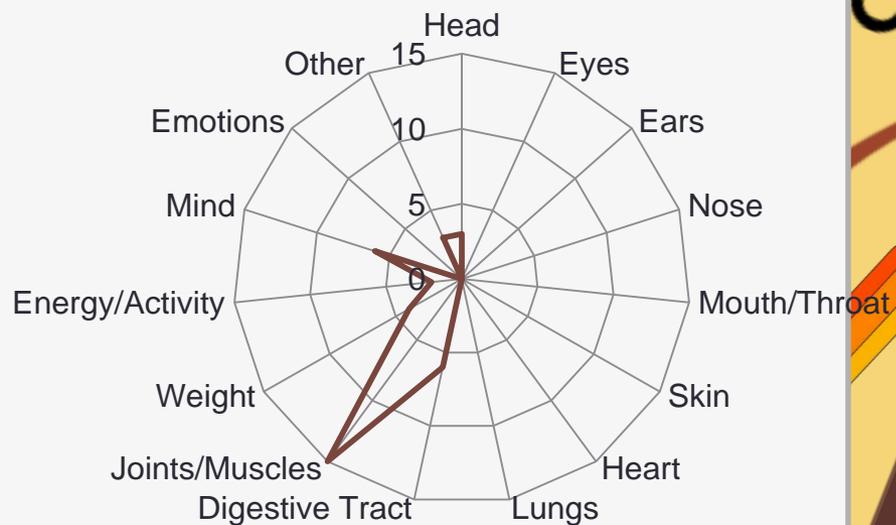
Labs

(normal range)

Visit 1

hsCRP (0 – 3 mg/l)	32.40 (↑)
Ferritin (15 – 150 ng/dl)	136 (WNL)
Fibrinogen (199 – 504 mg/dl)	460 (WNL)
IL-6 (0-15.3 pg/ml)	3.64 (WNL)
ESR (0 – 32 mm/Hr)	28 (WNL)
BNP (0 – 100 pg/ml)	57 (WNL)
Omega-3 index (>/=5.5 %by weight)	4.9 (WNL)

Total MSQ Score = 39



Case #2: Baseline visit

Profile history & examination

Past medical & drug history

Initial labs and tests

Management plan

Week 4 follow-up

Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
10	5	5	8

Scale:
 1 – no pain
 10 – pain as bad as you can imagine

Brief Pain Inventory

In past 24-hours how much has pain interfered in your:

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
10	8	10	10	10	10	10

American Chronic Pain Association Quality of Life Scale

6

- Work/volunteer limited hours
- Take part in limited social activities on weekends

Case #2: Baseline visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Management plan:
integration of SPMs into patient care

Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests



10t

- 6 SPM softgels/day for 4 weeks
- Continue with other medications

Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests

Case #2: 4 week follow up visit

Profile history
& examination

Past medical &
drug history

Initial labs and
tests

Management
plan

Week 4 follow-
up

Complaints:

- Patient states there are positive changes over the past week
 - 5/10 severity back pain

Current therapy:

- SPMs 6 soft gels/day

On Examination:

- Slight improvement in ROM
- BP: 110/72mm Hg
- Pulse: 60/min regular
- Weight: 192lbs

Additional Notes:

- Mild improvement in back pain
- Pt shows signs of less pain when rising from seated position.

Management plan:

- Increase SPMs to 8 soft gels/day for ~4 weeks
 - Taper to maintenance dose of ~2 soft gels/day once clinical targets are met
- Continue to watch for and avoid dietary and environmental triggers of inflammation
 - obesity, body composition, glucose control, dietary sources, leaky gut, allergy, Infection
 - Utilize anti-inflammatory strategies as needed

Case #2: 4 week follow up visit

Profile history & examination

Past medical & drug history

Initial labs and tests

Management plan

Week 4 follow-up

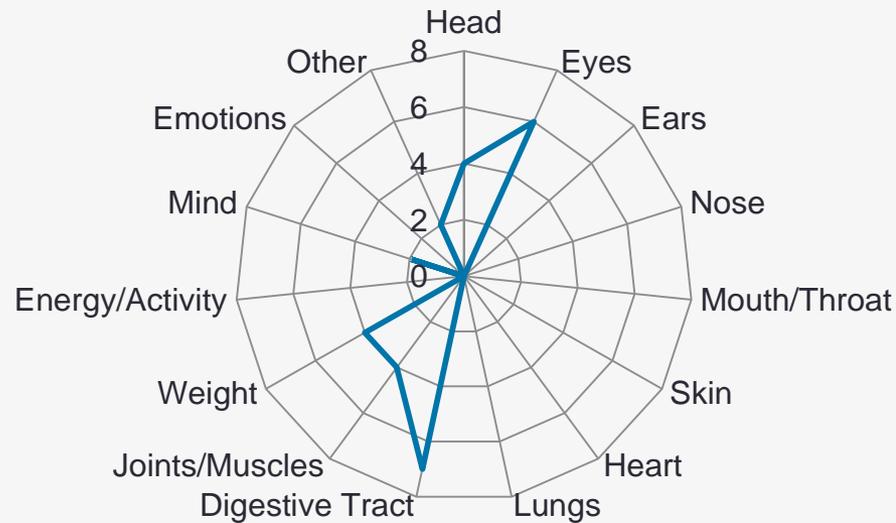
Labs

(normal range)

Visit 2

hsCRP (0 – 3 mg/l)	5.2
Ferritin (15 – 150 ng/dl)	95
Fibrinogen (199 – 504 mg/dl)	303
TNFa (0 – 8.1 pg/ml)	6.2
IL-6	2.16
ESR (0 – 32 mm/Hr)	11
BNP (0 – 100 pg/ml)	29
Omega-3 index (>/=5.5 %by weight)	4.2

MSQ Score = 29



Case #2: 4 week follow up visit

Profile history & examination

Past medical & drug history

Initial labs and tests

Management plan

Week 4 follow-up

Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
9	5	7	5

Scale:

- 1 – no pain
10 – pain as bad as you can imagine

Brief Pain Inventory

In past 24-hours how much has pain interfered in your:

- Scale from 1 (does not interfere) to 10 (completely interferes)

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
10	5	10	10	5	10	10

American Chronic Pain Association Quality of Life Scale

6

- Work/volunteer limited hours
- Take part in limited social activities on weekends

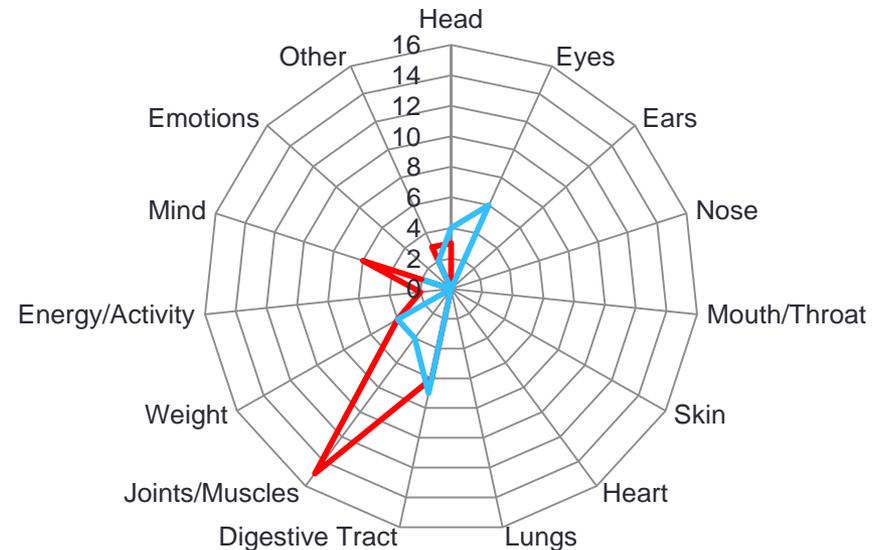
Case 2:

Summary of findings from baseline compared with 4 week follow up

Labs (normal range)	Visit 1	Visit 2
hsCRP (0 – 3 mg/l)	32.40	5.2 ↓
Ferritin (15 – 150 ng/dl)	136	95 ↓
Fibrinogen (199 – 504 mg/dl)	460	303 ↓
IL-6 (0-15.3 pg/ml)	3.64	2.16 ↓
ESR (0 – 32 mm/Hr)	28	11 ↓
BNP (0 – 100 pg/ml)	57	29 ↓
Omega-3 index (>/=5.5 %by weight)	4.9	4.2 ↓

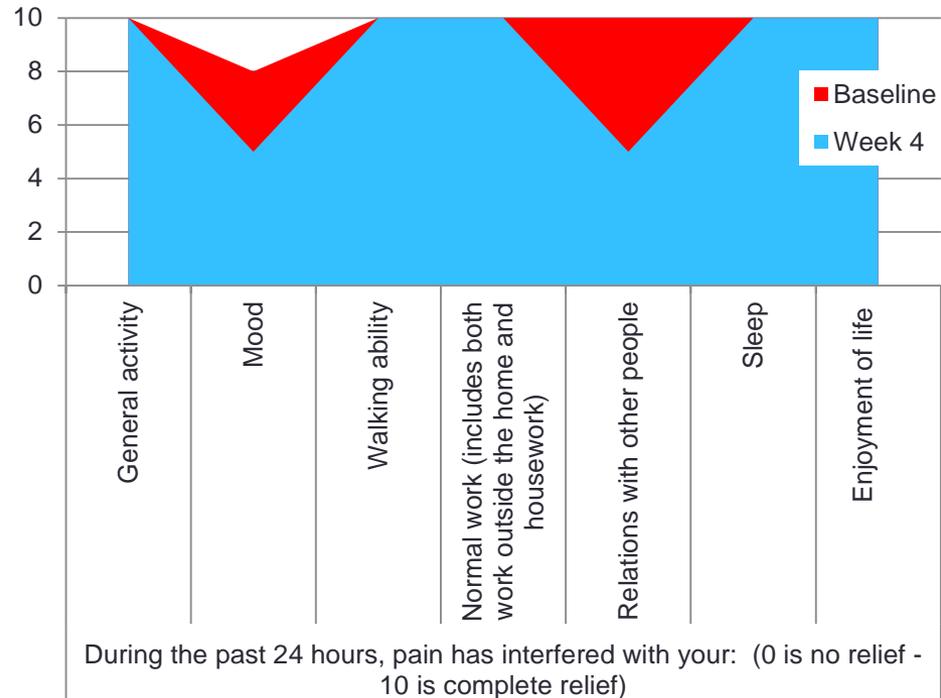
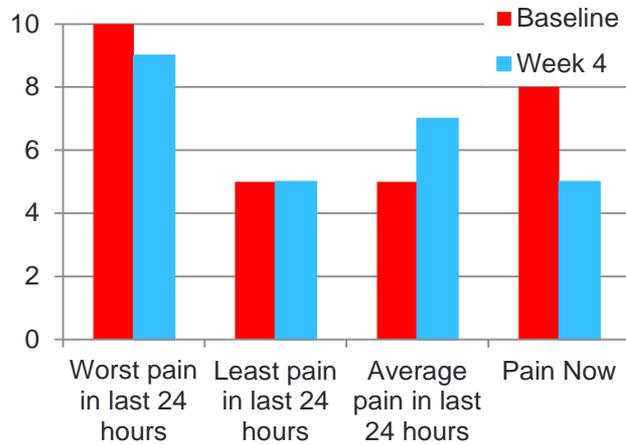
Baseline score = 39

Week 4 score = 29



Case 2:

Summary of findings from baseline compared with 4 week follow up



American Chronic Pain Association – Quality of Life Scale

Baseline

Score = 6

- Work/volunteer limited hours
- Take part in limited social activities on weekends

4 weeks

Score = 6

- Work/volunteer limited hours
- Take part in limited social activities on weekends

Specialized Pro-resolving Mediators: Evidence based innovation for managing chronic inflammation in clinical practice

Novel Solution and Pathway to Support Inflammatory Responses

- New Clinical Benefits to Resolve Inflammation
- Fills a Gap in Managing Inflammatory Responses

Two Independent yet Complementary Solutions to Managing Inflammatory Conditions

- Not Blocking, inhibiting or suppressing inflammation
- 'Resolves' inflammation to avoid prolongation to chronic health conditions

Proprietary Nutritional Solutions

- Specialized Pro-resolving Mediators
- Standardized Level of Activity

Clinical Uses with Superior Improvement in Ability to Resolve Inflammation

- Activates more effective resolution response
- Supports both normal inflammatory response AND its facilitated resolution

SPMs utilization: research is ongoing



Aspiration Pneumonia

RvE1 decreased cytokines and PMN infiltration and enhances LXA4 formation and bacterial clearance



Dry Eye

RvE1 analogue (RX-10045) reduce signs and symptoms



Periodontitis

LXs and RvE1 prevented PMN infiltration and connective tissue and bone loss



Arthritis

LXs inhibit edema formation and PMN influx, reduces TNF- α and LTB₄ levels
RvD1 possesses anti-hyperalgesic effects and decreases TNF- α and IL-1 β production

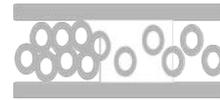


Type 2 Diabetes

RvD1 reduces macrophage accumulation, improved insulin sensitivity and promote healing of diabetic wounds
RvE1 and RvD1 ameliorate insulin sensitivity and reduce hepatosteatosis

Obesity

RvE1 and PD1 reduced adipokines and fatty liver and RvD1 reduced pro-inflammatory cytokines and stimulates M2 macrophages in adipose



Vascular Disease

RvD1 inhibited platelet aggregation and leukocyte-endothelial cell interactions and reduced size of myocardial infarction



Stroke

PD1 inhibits leukocyte accumulation and reduces infarct volume

Alzheimer's Disease

PD1 reduces AB42 cleavage and protected neurons from apoptosis. LSx reduce NF- κ B activation and stimulate alternative microglial cells



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QUESTIONS?
