Can we now explain medically unexplained symptoms?

Francis Creed
University of Manchester, UK

Hackett Award Lecture
APM Las Vegas
13th Nov 2009
### APM 56th Annual Meeting

**Disclosure: Francis Creed, MD**

<table>
<thead>
<tr>
<th>Company</th>
<th>Employment</th>
<th>Management</th>
<th>Independent Contractor</th>
<th>Consulting</th>
<th>Speaking &amp; Teaching</th>
<th>Board, Panel or Committee Membership</th>
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<td>Relationship is NOT considered directly relevant to the presentation.</td>
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*Note: Portions of the grid that are not needed can be grayed out. A good example might be when less than four companies are involved.*
Collaborators:

<table>
<thead>
<tr>
<th>Psychiatrists</th>
<th>Physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Else Guthrie</td>
<td>• David Thompson</td>
</tr>
<tr>
<td>• Nav Kapur</td>
<td>• Nick Read</td>
</tr>
<tr>
<td>• Arthur Barsky</td>
<td>• Lawrence Cotter</td>
</tr>
<tr>
<td>• Wayne Katon</td>
<td>• David Neary</td>
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<tr>
<td>• Judy Jackson</td>
<td>• Tony Lembo</td>
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<tr>
<td>• Maggie Fiddler</td>
<td><strong>Statisticians</strong></td>
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<tr>
<td>• Adrian Wells</td>
<td>• Barbara Tomenson</td>
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<tr>
<td><strong>Psychologists</strong></td>
<td>• Andrew Pickles</td>
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<tr>
<td><strong>Statisticians</strong></td>
<td><strong>Health economist</strong></td>
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<td><strong>Health economist</strong></td>
<td><strong>Stephen Palmer</strong></td>
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</tbody>
</table>
Medically unexplained symptoms

Kroenke & Price 1993, Nimnuan and Wessely, 2000

- Joint pains
- Back pain
- Headache
- Fatigue
- Gastroenterology
- Rheumatology
- Neurology

- Chest pain
- Arm/leg pain
- Abdominal pain
- Dizziness
- Irritable Bowel Syndrome
- Fibromyalgia
- Headache, Chronic Fatigue
Medically unexplained symptoms

Kroenke & Price 1993, Nimnuan and Wessely, 2000

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- Irritable Bowel Syndrome
- Fibromyalgia
- Headache, Chronic Fatigue
Medically unexplained symptoms

• How common are they?
• Primary care: 15-19%
• Medical out-patients: 35-52%

Burton C. British Journal of General Practice 2003;
Nimnuan Journal of Psychosomatic Research 2001
Hamilton J Journal of the Royal College of Physicians 1996.
Kooiman CG Psychosomatic Medicine 2000
### Medically unexplained symptoms in medical out-patient clinics

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>% unex</th>
<th>Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimnuan 2001</td>
<td>550</td>
<td>52%</td>
<td>Gynaecology, Neurology, Cardiology, Gastroenterology</td>
</tr>
<tr>
<td>Van Hemert 1993</td>
<td>191</td>
<td>52%</td>
<td>General medical</td>
</tr>
<tr>
<td>Hamilton 1996</td>
<td>324</td>
<td>35%</td>
<td>Neurology, Cardiology, Gastroenterology</td>
</tr>
<tr>
<td>Fiddler 2004</td>
<td>295</td>
<td>39%</td>
<td>Gastroenterology</td>
</tr>
<tr>
<td>Kooiman 2004</td>
<td>695</td>
<td>39-50%</td>
<td>General Medicine</td>
</tr>
</tbody>
</table>
Hypochondriasis
Pronounced worry about health and illness

Somatisation
High number of symptoms

Medically Unexplained symptoms
Medically Unexplained symptoms

Hypochondriasis
- Pronounced worry about health and illness

Somatisation
- High number of symptoms

Functional Somatic Syndromes
- Irritable Bowel S
- Chronic Fatigue S
- Fibromyalgia
Medically Unexplained symptoms

Functional Syndromes
IBS, CFS...

Somatisation
High number of symptoms
Hypochondriasis
Illness worry

Anxiety & depression
ICD diagnosis:
“Signs, symptoms & ill-defined conditions” (ICD codes 780-789)

- **UK NHS**: most costly diagnostic category of out-patients
- **4th** most expensive category in 10 care
- **Netherlands**: 5th most expensive category
- **USA**: 5th most frequent reason for clinic visits (60 million per annum)
Medically unexplained symptoms

• Common in primary care and in medical out-patients
• Associated with high costs

= Major problem in medicine!

Generally not well managed
Medically unexplained symptoms
100 consecutive medical out-patients

- Psychotropic medication 7%
- Lifestyle advice 8%
- Specialist nurse 1%
- Symptomatic medication 26%
- Further review 14%
- No action/no recommendation 44%

Mangwana et al INT’L. J. PSYCH IN MED. 2009 39; 33-44
Practice point

• Don’t let internists/primary care doctors think that all patients with MUS should see a psychiatrist - you will never go home at night!

• Do spend time helping internists/primary care doctors to develop their skills in managing these patients
MUS a major problem in medicine

- Why such little progress in explaining?
- DSM definition of Somatisation disorder
- Dualism - separating mind & body

- The way ahead
- A Psychosomatic perspective
- A New Classification?
MUS a major problem in medicine

- Why such little progress in explaining?
- DSM definition of Somatisation disorder
- 3 problems:
  - Wrong threshold
  - “MUS” difficult to measure
  - “MUS” reinforces dualism
No. of bodily symptoms required for diagnosis

- Briquet’s syndrome
- DSM-III: 12(m) 14(f)
- DSM IV: 8 symptoms
- Undiff Som Dis: 1 symptom

The University of Manchester
No. of bodily symptoms required for diagnosis

- Briquet’s syndrome
- DSM-III 12(m) 14(f)
- Prev=0.4% population

The University of Manchester
No. of bodily symptoms required for diagnosis

- Briquet’s syndrome
- Multisomatoform Disorder 3 in 2 weeks
- Abridged Somatisation 4 m / 6 f

The University of Manchester
Prevalence of these disorder in primary care

- Abridged somatisation (4m/6f) 6%
- Multisomatoform disorder 24%
- DSM IV somatization disorder <1%
- DSM IV Undifferentiated somatoform disorder 79%

Lynch DJ et al  Prim Care Companion J Clin Psychiatry 1999
206 high-utilising MUS patients:

Smith et al Psychosom Med. 2005

- Of 206 high-utilising MUS patients:
- 4.4% any DSM-IV somatoform diagnosis
- (+ 18.9% - abridged somatisation disorder)
- 60.2% - anxiety or depression diagnosis without DSM-IV somatoform diagnosis
119 distressed high-utilising patients:
Katon et al Gen Hosp Psych 1990

• Of 119 distressed high-utilising MUS patients
  - mean of 8.7 medically unexplained symptoms:
• 20.2% - DSM-III-R Somatisation disorder
• 73% - Abridged (4/6) criteria of somatisation
What’s taken you so long, Francis?
Abridged!
Medically Unexplained symptoms

Functional Syndromes
IBS, CFS...

Somatisation
High number of symptoms

Hypochondriasis
Illness worry

Anxiety & depression

DSM Somatisation disorder
Practice point

- How do we diagnose patients with multiple bodily symptoms?

- Many have depression and/or anxiety but this diagnosis may not do justice to their treatment needs
DSM Somatoform disorders

- Pain disorder
- Somatisation disorder
- Hypochondriasis

Anxiety & depression
DSM-IV Definition of somatisation disorder

- “Multiple physical complaints ...............:
- cannot be fully explained by known medical condition (after full investigation)

<table>
<thead>
<tr>
<th>Difficult to measure:</th>
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<tbody>
<tr>
<td>Been to Dr?</td>
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<tr>
<td>Not caused by medical illness</td>
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</tbody>
</table>
Somatoform disorders

- Not included in National Surveys of mental health

* USA - National Comorbidity Survey. Kessler RC et al 1994
* USA - National Comorbidity Survey replication. Kessler 2005
* Australia - National Mental Health Survey. Andrews G. 2001
* Netherlands – NEMESIS. Bijl SPPE 1998
* World Mental Health Surveys: Kessler. JAMA 2004
Somatoform disorders

- Psychiatrists and health service planners tend to neglect these disorders

Somatization … a forgotten public health agenda?
Saxena S In Somatoform disorders. 2005

Creed F. World Psychiatry Oct 2006
Somatoform disorders

German group that has included somatoform disorders

“…… astonishing considering that these disorders are the third most frequent in the general population”

Baumeister SPPE 2007.
MUS a major problem in medicine

- Why such little progress in understanding?
- Definition of Somatisation disorder

<table>
<thead>
<tr>
<th>Rare in primary Care/population</th>
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<tr>
<td>Difficult to measure</td>
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<tr>
<td>Omitted from epidemiological research</td>
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</table>
MUS a major problem in medicine

- Why such little progress in explaining?
- Definition of Somatisation disorder
- Dualism - separating mind & body
Medically unexplained??
Medically unexplained??

Patient - post laparotomy for abdominal pain, weight loss & diarrhoea:
“Well, Mrs S. there is absolutely nothing wrong with you – its all psychological”
Its all organic

Its all psychological

organic

psychological
The term: “Medically unexplained symptoms”

- Negative definition - defines group by what it is not
- Reinforces the “either/ or” notion - that symptoms are either due to organic disease or something else.

- Creed et al: Is there a better term than “Medically unexplained symptoms”? J Psychosom Res in press
Its all organic

Irritable bowel syndrome

Its all psychological
Its all Organic!

Irritable Bowel Syndrome: a little understood organic bowel disease?
Talley & Spiller Lancet 2002

"IBS… in the past relegated to the realm of psychosomatic and unimportant….

..colonic flora might be abnormal ..”

Inflammation … could contribute to diarrhoea…
Its all organic

Evidence for pure organic aetiology is weak
Links to GI infection
GI inflammation

Psychological factors not limited to
treatment seeking
Abnormal processing of pain

Its all psychological
Its all organic

Its all psychiatric
<table>
<thead>
<tr>
<th>No. of somatic symptoms</th>
<th>% dep or anx</th>
</tr>
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<tbody>
<tr>
<td>1,2</td>
<td>10</td>
</tr>
<tr>
<td>3,4</td>
<td>20</td>
</tr>
<tr>
<td>5,6</td>
<td>30</td>
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<tr>
<td>6,7,8</td>
<td>40</td>
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<tr>
<td>9+</td>
<td>90</td>
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Number of somatic symptoms & % with anxiety/depressive disorder

Number of somatic symptoms & % with anxiety/depressive disorder

Patients with 9+ bodily symptoms – 78% have anx/depr.

% anx/dep
6-8 sympts = 52%
4-5 sympts = 32%

Association of Functional Syndromes with Depression and Anxiety

- Meta-analysis of 244 studies:
  - IBS, CFS, Fibromyalgia
- Syndromes clear association with depression and anxiety

- Effect size was small to moderate – unexplained symptoms often arise without anxiety or depression

Henningsen et al Psychosom Med 2002
Post-viral fatigue
Wessely et al Lancet 1995

• Follow up study of primary care patients
  ➔
  • No association between infection and later chronic fatigue.

• “common infections play little part in the aetiology of chronic fatigue syndrome”
Post-infective chronic fatigue
Hickie et al BMJ 2006

• Follow-up study of patients with Epstein-Barr and other viral infections

• → 11% developed chronic fatigue syndrome

• CFS was predicted by severity of viral infection not psychological factors
Post-infective chronic fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to chronic fatigue syndrome.
Psychiatric disorder only in some patients with MUS
What other factors?
MRC 1946 birth cohort study
Multiple Symptoms aged 36 years
Hotopf et al, Am J Psych 1999

• Poor parental health aged 15 years associated with multiple bodily symptoms aged 36 years (adjusted for current psychiatric disorder)

Psychiatric disorder is also a predictor....
Psychiatric disorder and Multiple Symptoms
Hotopf et al, Am J Psych 1999

Population attributable risk: Psychiatric disorder as a cause of bodily symptoms = 40.3%
Therefore psychiatric disorder is unlikely to be the sole explanation for most cases
Psychiatric disorder and Multiple Symptoms
Hotopf et al, Am J Psych 1999

Population attributable risk: Psychiatric disorder as a cause of bodily symptoms = 40.3%
Therefore psychiatric disorder is unlikely to be the sole explanation for most cases
### Psychiatric disorder and Multiple Symptoms

Harvey & Wessely. J Psychosom Res 2009

<table>
<thead>
<tr>
<th>Age 36 yrs</th>
<th>Age 43 yrs</th>
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<tbody>
<tr>
<td>Free of Fatigue or Psychiatric Disorder (n=3011)</td>
<td>Neither psych dis. or fatigue</td>
</tr>
<tr>
<td></td>
<td>Fatigue alone (n=201)</td>
</tr>
<tr>
<td></td>
<td>Fatigue + Psych Dis (n=164)</td>
</tr>
<tr>
<td></td>
<td>psych dis alone</td>
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</tbody>
</table>
Psychiatric disorder and Multiple Symptoms
Harvey & Wessely. J Psychosom Res 2009

Age 36 yrs
“energetic” child
Overweight 36 yrs
neuroticism

Age 43 yrs
Compared:
Fatigue alone (n=201)
Fatigue + Psych Dis (n=164)

FH Psych dis.
-ve life events
neuroticism
It's not all psychiatric.
Practice point

• Do not get caught in a mind v body argument with patients.
• I disallow “its all in the mind” and point out that modern research shows that we cannot separate mind and body.
• We need models to explain this to patients, e.g. heart rate when faced with danger, pain worse with depression, tense muscles etc…
Medically Unexplained symptoms

Functional Syndromes

CFS

Fatigue alone

Fatigue + Psych Dis

Somatisation
High number of symptoms

Hypochondriasis
Illness worry

Anxiety & depression
Psychiatric disorder is only partial explanation:
- Illness in parent while a child
- Other factors
- Improvement from Psychological therapy?
CBT for somatization and symptom syndromes: Systematic Review


- 29 RCTs (back, chest pain, CFS, IBS etc)
- CBT → overall improvement compared to controls: for Bodily symptoms & functional status

- Beneficial effects of CBT seem to occur independent of improvement in psychological distress
Changes in cognitions 6 months after 1\textsuperscript{st} consultation (105/110)

\textit{Van Dulmen Psychol Med 1997}

- Improvement in abdominal complaints associated with:
  - less anxiety (\(p<0.01\))
  - less fear of cancer (\(p=0.02\)) and
  - greater attribution to stress (\(p=0.04\))
  - Catastrophised less (\(p=0.002\))

- Outcome not related to number of consultations or investigations
Irritable bowel syndrome
Cognitive Behaviour Therapy

• CBT $\rightarrow$ Improved global well being with little change in pain
• “the pain is still there but I manage it better” (better coping)

Drossman et al Gastroenterology 2003; 125:19-31
Chronic Fatigue Syndrome
Prins et al Lancet 2006
Intensive CBT \(\rightarrow\) improvement

The positive effect of CBT for CFS is related to changes in illness related cognitions and self-efficacy

After prolonged rest… exercise is painful …
…therefore exercise is damaging
I know that this illness will never improve…
There is nothing I can do to improve my state of health
Psychiatric disorder only **partial** explanation of bodily symptoms

* Illness in parent during childhood
* Benefit from Psychological therapy suggests cognitive factors
Practice point

• Always ask patients “what do you think causes these symptoms?”
• Explore fears of serious illness and the relationship to:
  a) previous (viral) illness
  b) stress
• Simple explanation may be very helpful to patients........keeping a diary of symptom severity may also help.
Practice point

- Do not aim to “cure” or greatly reduce pain or fatigue if they are chronic – aim to increase functioning and decrease healthcare use.
- Explain the deleterious effects of avoidance (exercise in CFS/fibromyalgia; food avoidance in IBS)
Antidepressant therapy for unexplained symptoms and syndromes. Systematic Review


• 94 RCTs (headache, fibromyalgia, IBS etc)
• 48 studies → meta-analysis response of unexplained physical symptoms – antidepressants superior to placebo: pooled OR = 3.4 (95%CI: 2.6-4.5)

• Beneficial effects of antidepressant seemed to occur independent of improvement in psychological distress
Randomised Controlled Trial


257 IBS patients.

- **Psychotherapy** (8 sessions) n=85
- Antidepressant Paroxetine n=86
- Treatment as usual n=86

Baseline

Outcome at

3m

15m
Overall result

Creed et al *Gastroenterology* 2003 124: 303-317

- In the long-term:
  - Antidepressant and psychotherapy →

- **Significant improvement** in:
  - Health status at no additional costs

- But this result cannot be explained simply by improved *abdominal pain and depression*
Severe Irritable Bowel Syndrome (n=227)

Chronic fatigue Neurasthenia (n=88)

Somatisation
High number of Symptoms
SCL-90 Som (65)

Depressive Disorder (74)

Respond to psychotherapy

Respond to Antidepressant
Practice point

- In patients with Irritable bowel syndrome + depressive disorder:
  - If depressive disorder is adequately treated → reduced pain and improved quality of life.
  - So must treat depression energetically
  - SSRI > psychotherapy in reduction of depression at 3 months
Psychiatric diagnosis (n=257)

- 29% depressive disorder
- 12% panic disorder [41.6%]
- 14% gen. anxiety disorder
- 9% hypochondriasis
- 12% severe 23% touch sex abuse
- 25% top quartile somatisation
- 35% neurasthenia
Severe Irritable Bowel Syndrome (n=227)

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Psychiatric diagnosis (n=257)

- 29% depressive disorder
- 12% panic disorder  
- 14% gen. anxiety disorder
- 9% hypochondriasis
- 12% severe 23% touch sex abuse — mediated by
- 25% top quartile somatisation
- 35% neurasthenia
Conclusion re history of sexual abuse

- Patients with a reported history of sexual abuse do particularly well with psychotherapy (NB small numbers)
- Change mediated by somatisation
Depressive disorder (29%): 35 resolved 47 unresolved – change on Hamilton Rating Scale
Depressive disorder - resolved v unresolved: Abdominal pain VAS

p=0.019
Depressive disorder - resolved v unresolved: SF36 role limitation score

p<0.001
Total costs for 12 months after treatment *

- 0.5
- 1
- 1.5
- 1.5 +

* adj for age, sex, education, depression, panic and GAD abuse history, baseline SF-36 PCS

Psychotherapy
Antidepressant
Rx as usual
Severe Irritable Bowel Syndrome (n=227)

Chronic fatigue Neurasthenia (n=88)

35

Somatisation
High number of Symptoms SCL-90 Som (65)

12

22

Depressive Disorder (74)

10

19

23

Respond to psychotherapy

Respond to Antidepressant

The University of Manchester
Severe Irritable Bowel Syndrome (n=227)

- Chronic fatigue Neurasthenia (n=88)
  - 35
  - 7
  - 12
  - 4
  - 19
  - 2

- Somatisation
  - High number of Symptoms
  - SCL-90 Som
    - 22
    - 9
    - 10
    - 3
    - 21
    - 5

- Depressive Disorder (74)
  - 23
  - 3

Total:
- 77
- 19
- 44
- 12
- 101
- 74
Practice point

- Unexplained symptoms/syndromes respond to antidepressants
- And / or CBT.
- If one doesn’t work try the other or combination
MUS a major problem in medicine

- Why such little progress in explaining?
- Definition of Somatisation disorder
- Dualism - separating mind & body
- The way ahead
- A Psychosomatic perspective
- A New Classification?
Its all organic

Psychosomatic!

Its all psychological
Its all organic

Psychosomatic

It's all psychological

a) onset
Aetiological model of IBS

- Inflammation – post infective
- Psychological factors
- Data suggest an interaction between infection and psychosocial factors
Correlates of new onset post-infective IBS

**EC cells:**
1-sd increase 3.8-fold (95% CI, 1.3–7.5)

**HADS anxiety & depression**
1-sd increase 3.2-fold (95% CI, 1.8–8.2)

OR = 3.8

Post-infective IBS

OR = 3.2

Dunlop et al. Gastroenterology 2003; 125: 1651-9
Aetiological model of IBS

- Inflammation – post infective specific?
- Psychiatric symptoms

and

IBS
Specificity hypothesis
Moss Morris 2006

Acute illness
Campylobacter gastroenteritis → 6 months
11% IBS
5% Chronic fatigue

Infectious mononucleosis. → 8% IBS
8% CF
Infection and anxiety predict IBS/CFS

Moss Morris 2006

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with Campylobacter IBS</td>
<td>3.3 (1.6 – 6.4)</td>
<td>2.4 (1.2 – 4.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.4 (1.4 – 3.9)</td>
<td>1.8 (1.05 – 3.2)</td>
</tr>
<tr>
<td>Infectious Mononucleosis CFS</td>
<td>2.6 (1.0 – 7.1)</td>
<td>1.3 (0.5 – 3.2)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.6 (1.5 – 6.9)</td>
<td>2.6 (1.2 – 5.3)</td>
</tr>
</tbody>
</table>
Aetiological model of CFS

Post infective (IM)

- Psychological factors

Associated with persistence also?
Population-based study of functional somatic syndromes (n=632)

- Predictors of persistent CWP:
- SSI (numerous somatic symptoms)

- Predictors of persistent chronic fatigue: childhood abuse, Neuroticism, depression & SSI (number of somatic symptoms).
Post-infective IBS & CFS?

Psychosomatic model - onset

• But only c. 14% of IBS patients have post-infective IBS.

• Same in Chronic fatigue syndrome?

• One pathophysiological pathway to chronic fatigue syndrome.
Its all organic

Psychosomatic

b) All patients

Its all psychological
• Include all patients?
• …with Medically Unexplained symptoms
• and
• … with symptoms are explained by organic disease?
Medical out-patients: Neurology, Cardiology & Gastroenterology

Fiddler et al Gen Hosp Psych 2004
Jackson et al J Psychosom Res. 2006

- **181** - **organic** - Multiple Sclerosis, stroke, ischaemic Heart Disease, inflammatory bowel disease
- **114** - **MUS** - headaches, neck/ limb pain, fatigue, parasthesiae, chest pain, breathlessness, irritable bowel syndrome, functional dyspepsia
Number of bodily symptoms by patient diagnostic group
Fiddler et al Gen Hosp Psych 2004

medically unexplained (n=114)  expl. by organic disease (n=181)

Means (sd)  7.7 (3.0)  7.5 (2.8)
Number of bodily symptoms - childhood adversity and anx/dep as risk factors
Fiddler et al Gen Hosp Psych 2004

![Bar chart showing the number of bodily symptoms in mus and organic categories for different groups: Ad- Dep-, Adv +, Dep+, Ad+ Dep+, with p-values of 0.002 and <0.0005 for mus and organic respectively.](chart.png)
Dr visits increases with number of bodily symptoms

No. dr Visits Adjust. for Age, sex, Anx & depn

MUS

Organic

0 to 5
6 to 7
8 to 9
10 to 12
Health status impaired with many bodily symptoms

SF36
PCS
Adjust. for
Age, sex, Anx & depn

MUS
Organic

0 to 5  6 to 7  8 to 9  10 to 12
# Predictors of health status

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>*</td>
</tr>
<tr>
<td>Mus v organic</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiety</td>
<td>**</td>
</tr>
<tr>
<td>Depression</td>
<td>**</td>
</tr>
<tr>
<td>Somatic symptom score</td>
<td>***</td>
</tr>
<tr>
<td>Fear of illness and death</td>
<td>***</td>
</tr>
<tr>
<td>Health worry &amp; preoccupation</td>
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</tbody>
</table>

- SF36
- PCS
- 6 months

Fidler et al, Gen Hosp Psych, 2004
Medically Unexplained symptoms

Processes that affect all patients

Functional Syndromes
IBS, CFS...

Somatisation
High number of symptoms

Hypochondriasis
Illness worry

Anxiety & depression
All patients

Functional Syndromes
- IBS, CFS...

Somatisation
- High number of Symptoms

Health anxiety

Anxiety & depression

General medical illnesses

Outcomes
- Impairment
- Healthcare use

Outcomes
- High
- Impairment
- Healthcare use
### Predictors of frequency of consultation at primary care (n=738)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95%)</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Female sex</td>
<td>(1.45) ***</td>
<td></td>
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<tr>
<td>Chronic physical illness</td>
<td>(1.60) ***</td>
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<tr>
<td>Chronic psychiatric illness</td>
<td>(1.43) ***</td>
<td></td>
</tr>
<tr>
<td>Somatic symptom score</td>
<td>(1.14) ***</td>
<td></td>
</tr>
<tr>
<td>IAS illness behaviour score</td>
<td>(1.33) ***</td>
<td></td>
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<tr>
<td>IAS health anxiety scale</td>
<td>(1.12) ***</td>
<td></td>
</tr>
</tbody>
</table>

Kapur N et al Psychol Med 2004

No. of GP-patient contacts (home or clinic) over subsequent year
Childhood experiences and consultations at primary care

<table>
<thead>
<tr>
<th>Experience</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Adult psychiatric illness</td>
<td>8.5</td>
<td>3.2-22.5</td>
</tr>
<tr>
<td>Any childhood abuse</td>
<td>&lt;0.0001</td>
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<tr>
<td>Maternal physical illness</td>
<td>24.4</td>
<td>2.8-219.2</td>
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<tr>
<td>Serious childhood illness</td>
<td>7.4</td>
<td>1.8-30.7</td>
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<tr>
<td>Parental indifference/neglect</td>
<td>11.4</td>
<td>2.1-62.3</td>
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<tr>
<td>Illness in sibling</td>
<td>22.9</td>
<td>1.7-300.5</td>
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<tr>
<td>Paternal psychiatric illness</td>
<td>0.002</td>
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<tr>
<td>Sex</td>
<td>0.19</td>
<td>0.03-1.0</td>
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</table>

Frequent (top decile) Attenders

Random Selected controls

Kapur N et al Brit J Psych 2004
All patients

Functional Syndromes
IBS, CFS

Somatisation
High number of Symptoms

Health anxiety

Anxiety & depression

General medical illness

Trigger
Life events
Onset of Psych. or Phys. disease

Outcomes
Impairment
High Healthcare use

Predisposing
Genetic

Childhood Ill parent Abuse

Adult Neuroticism
Chronic Phys. disease

Outcomes
Impairment
High Healthcare use
Extra-intestinal symptoms:
- headaches, backaches, bad breath, fatigue, dizziness, weakness, tightness in chest

% with high Somatisation

Chronic fatigue syndrome

Fibromyalgia

Irritable bowel syndrome

30%

30%

37%
Correlates of Extra-intestinal symptoms

- 3,048 participants (twins), 371 (12.2 %) fulfilled Rome II criteria for IBS;

- Logistic regression → EIS
- Age, sex, BMI
- MDD, GAD, Panic disorder, Neuroticism (all \( p < 0.0005 \))
- Fatigue, muscular pains, GERD, dyspepsia, IBS (all \( p < 0.0005 \))

Lembo et al Am J Gastro 2009
<table>
<thead>
<tr>
<th></th>
<th>Monozygotic</th>
<th>Dizygotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 3,048</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ns</td>
<td></td>
<td>ns</td>
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<tr>
<td>gender ns</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Co-twin has EIS ≥ 12</td>
<td>6.82 (4.4 – 10.4)</td>
<td>2.71 (1.7 – 4.4)</td>
</tr>
<tr>
<td>Neuroticism 1.14 (1.1 – 1.2)</td>
<td>1.27 (1.2 – 1.4)</td>
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<tr>
<td>Psych. Dis. 4.17 (2.3 – 7.6)</td>
<td>3.15 (1.8 – 5.6)</td>
<td></td>
</tr>
<tr>
<td>IBS 2.82 (1.7 – 4.6)</td>
<td>1.95 (1.1 – 3.3)</td>
<td></td>
</tr>
</tbody>
</table>

Lembo et al Am J Gastro 2009
Genetics
Gillespie et al Psychol Med 2000

Most genetic and environmental variance of somatic distress is shared with depression and phobic anxiety but

• “33% of genetic variance in somatic distress due to a specific gene action unrelated to depression or phobic anxiety”
• and
• “74% of individual environmental influences on somatic distress also unrelated to depression or phobic anxiety”
Medically Unexplained symptoms

Functional Syndromes
IBS, CFS...

Somatisation
High number of symptoms

Hypochondriasis
Illness worry

Anxiety & depression
MUS a major problem in medicine

- Why such little progress in explaining?
- Definition of Somatisation disorder
- Dualism - separating mind & body
- The way ahead
- A Psychosomatic perspective
- A New Classification?
DSM-V workgroup
Somatic Symptom disorders

Joel Dimsdale
• Arthur Barsky
• Francis Creed
• Javier Escobar
• Nancy Frasure-Smith
• Michael Irwin
• Francis Keefe
• Sing Lee
• James Levenson
• Michael Sharpe
• Lawson Wulsin
DSM Somatoform disorders

Pain disorder

Somatisation disorder

Hypochondriasis

Anxiety & depression
Proposed changes in DSM-V

Somatic Symptom disorders

- Elimination of “medically unexplained” symptoms as a diagnostic criterion
- Somatisation,
- Hypochondriasis,
- Pain disorder

DSM IV Somatoform disorders

- Pain disorder
- Somatisation disorder
- Hypochondriasis
- Anxiety & depression
Hypochondriasis
Pronounced worry about health and illness

Somatisation
High number of symptoms

Medically Unexplained symptoms
Barsky score for hypochondriasis /somatisation
Med care 2001;39: 705-715

- total score - items are weighted scores for:
  - somatic symptoms,
  - disease fear,
  - bodily preoccupation,
  - disease conviction
- these are the 4 component symptoms of hypochondriasis.

identified top 14% of primary attenders
Per Fink
Research Clinic for Functional Disorders and Psychosomatics
Aarhus University Hosp., Denmark.
A New, Empirically Established Hypochondriasis Diagnosis

Fink et al Am J Psychiatry 2004

Classification allowed definition of new diagnostic criteria for hypochondriasis......

In 75.9% of the patients with severe class 1 hypochondriasis, the primary care physicians reported - patient frequently consulted because of medically unexplained functional symptoms.
Population-based – Health anxiety & numerous bodily symptoms

% 4+ visits in subsequent year (control= 14.5%)

- 29.9%: High health Anxiety Only (n=67)
- 36%: High on both scales (n=50)
- 26.6%: High number of bodily symptoms only (n=64)
Medically Unexplained symptoms

**Predisposing**
- Genetic
- Childhood
  - Ill parent
  - Abuse
- Adult
  - Neuroticism
  - Chronic
  - Phys. disease
  - support

**Functional Syndromes**
- IBS, CFS..

**Somatisation**
- High number of Symptoms

**Health anxiety**

**Anxiety & depression**

**Trigger**
- Life events
- Onset of Psych. or Phys. disease

**Outcomes**
- Impairment
- High Healthcare use

**Life events**

**Neuroticism**

**Chronic**

**Phys. disease**

**support**

**High number of Symptoms**

**Healthcare use**
DSM Somatoform disorders

- Somatisation disorder
- Pain disorder
- Hypochondriasis

Anxiety & depression
Proposed changes in DSM-V
Somatic Symptom disorders

- Elimination of “medically unexplained” symptoms as a diagnostic criterion
- Somatisation,
- Hypochondriasis,
- Pain disorder
- If depressive disorder co-exists code both

Proposed changes in DSM-V
Somatic Symptom disorders

- New way of thinking
- What are the chances it will catch on?
• Interesting to old age psychiatrists?
Not sure!
• Of interest to those concerned with high healthcare costs and ways of reducing them?
Unimpressed
Interesting for those concerned with physical disease and comorbid depression?
Interesting
Can we explain medically unexplained symptoms?

- Wrong question – shouldn’t try and define group of patients which is poorly defined and heterogeneous
- Should define the processes that lead to poor outcomes (impaired functioning and high health use);
- If we understand the origin of these processes and how they can best be treated we will improve our care of all patients with numerous somatic symptoms not just those which are described as “medically unexplained"
Key references

- L. Wulsin & J. Dimsdale: DSM-V for Psychosomatic Medicine: Current Progress and Controversies
- Recent research: J Psychosom Res Special Issue April 2010
Its all organic

Its all psychological

Medically unexplained??
Psychosomatic

Measure all symptoms not just medically unexplained

Its all organic

Its all psychological

organic

psychological
# DSM-V project Collaborating Centres

“A dimensional approach to diagnosis of somatisation in DSM-V”

<table>
<thead>
<tr>
<th>Centre</th>
<th>Investigator(s)</th>
<th>No of Subjects</th>
<th>Age</th>
<th>Measure</th>
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<tbody>
<tr>
<td>Bremen</td>
<td>Cecilia Essau</td>
<td>1035</td>
<td>12-17</td>
<td>SCL-90_R</td>
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<tr>
<td>Basel</td>
<td>R Lieb</td>
<td>1995</td>
<td>14-24</td>
<td>CIDI</td>
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<td>Aarhus</td>
<td>P Fink</td>
<td>1457</td>
<td>18-70</td>
<td>SCL-90</td>
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<td>Dresden</td>
<td>F Jacobi</td>
<td>4181</td>
<td>17-66</td>
<td>Zerssen</td>
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<td>Groningen</td>
<td>J Rosmalen</td>
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<td>33-79</td>
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<td>Manchester</td>
<td>FHC/ JB</td>
<td>1443</td>
<td>25-65</td>
<td>SSI</td>
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<td>Sri Lanka</td>
<td>Athula</td>
<td>6119</td>
<td>18-75</td>
<td>PHQ</td>
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<td>18-91</td>
<td>CIDI</td>
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<tr>
<td>Marburg</td>
<td>W Rief</td>
<td>2510</td>
<td>14-93</td>
<td>PHQ</td>
</tr>
</tbody>
</table>

Francis Creed & Barbara Tomenson + collaborators
Females have significantly more symptoms than males for both MUS and MES, but for medically explained symptoms there is a significant increase with age (p<0.001), which is not at all significant for MUS (p=0.49). There is no significant age group by sex interaction for either MUS or MES.
Medically unexplained medically explained
adjusted for physical illnesses

Oslo - Kari Ann Leiknes
Number of Medically Unexplained Symptoms out of 42
adjusted for number of physical diseases (out of a checklist of 13)

Oslo - Kari Ann Leiknes
Number of Medically Explained Symptoms out of 42
adjusted for number of physical diseases (out of a checklist of 13)
Difference between the sexes is significant at p<0.001

- *Oslo*, adjusted for age and depression & physical disorders. This is true for both MUS and MES.

- *Dresden*, adjusted for MDD, panic, anxiety, and physical illnesses

- *Groningen*, adjusted for MDD, panic, anxiety, and physical illnesses. This is true for both MUS and MES.

- *Sri Lanka*, adjusted for age and physical diagnosis.

- *Manchester* adjusted for physical illness, anxiety & depression
Correlation between the number of medically unexplained symptoms and all symptoms

- Few bodily symptoms: $r = 0.721; p \leq 0.001$
- Many bodily symptoms: $r = 0.703; p \leq 0.001$
Provisional conclusion

- We can readily measure all bodily symptoms.
- This may provide as reliable an indicator of the tendency to report bodily symptoms as measuring only medically unexplained symptoms.
- Need also other cognitive features?
DSM IV Somatoform disorders

- Somatisation disorder
- Pain disorder
- Hypochondriasis
- Anxiety & depression
Medically Unexplained symptoms

Functional Syndromes
CFS..

Somatisation
High number of symptoms

Hypochondriasis
Illness worry

Anxiety & depression

50%
All patients

Predisposing
- Genetic
- Childhood Ill parent * Abuse *
- Adult Neuroticism Chronic * Phys. disease

IBS, CFS.. Functional Syndromes

Somatisation
High number of Symptoms

Health anxiety

Trigger
- Life events
- Onset of Psych. * or Phys. disease

Depression Anxiety

Outcomes
- Impairment
- High Healthcare use
Predisposing -- mediating -- outcomes

**Predisposing**
- Genetic
- Childhood Ill parent Abuse
- Adult Neuroticism Chronic Phys. disease

**Functional Syndromes**
IBS, CFS...

**Somatisation**
High number of Symptoms

**Health anxiety**

**Anxiety & depression**

**Trigger**
- Life events
- Onset of Psych. or Phys. disease

**Outcomes**
- Impairment
- High Healthcare use
Medically Unexplained symptoms

Functional Syndromes
CFS...

Somatisation
High number of symptoms

Anxiety & depression
Prospective population-based study (n=1433)

Fibromyalgia: 30.1%
Somatisation (top 10%): 37.1%
Irritable bowel syndrome: 30.1%
Chronic fatigue syndrome: 30.1%
Medically Unexplained symptoms

Functional Syndromes
CF, IBS, CWP

Somatisation
High number of symptoms

Anxiety & depression

no FSS syndrome
Health-related quality of life by syndrome and somatisation (top 10%)

p<0.001 adjusted for age, sex, anxiety, depression

- no syndrome
- syndr no somatis
- syndrome + somatis
Dr visits by syndrome and somatisation (top 10%)

p<0.016 adjusted for age, sex (ns with deprn)
• Impairment and increased healthcare associated with both presence of Functional somatic syndrome (IBS, CF, fibromyalgia) and number of somatic symptoms.

• High number of somatic symptoms → powerful influence on outcomes
Medically Unexplained symptoms

Functional Syndromes
IBS, CFS...

Somatisation
High number of Symptoms

Health anxiety

Anxiety & depression

Trigger
Life events
Onset of Psych. or Phys. disease

Outcomes
Impairment
High Healthcare use
Change in Health status

- Age, (-0.11)
- Abuse (0.1)
- Unemployed (-0.19)
- Baseline SF36 PCS (0.37)
- Abdominal pain (-0.18)
- Change in abdominal pain (0.2)
- SCL somatisation (-0.32) (ch 0.3)
- SCL anxiety (0.28) (ch -0.2)
- Change in depression (0.14)
- Psychotherapy (0.16)
- Paroxetine (0.15)

SF36 Physical Component score at follow-up

Creed et al Aust NZ Psychiatry 2005; 39: 807-15
Change in Health status

- Age, (-0.11)
- Abuse (0.12)
- Unemployed (-0.19)

- Baseline SF36 PCS (0.42)
- Abdominal pain (-0.12)

- SCL somatisation (-0.18)
- Neurasthenia (-0.11)
- Depression (-0.20)

- Psychotherapy (0.21)
- Paroxetine (0.22)

SF36 Physical Component score at follow-up

Creed et al Aust NZ Psychiatry 2005; 39: 807-15
# Outcomes and treatments in IBS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Outcome</th>
<th>Optimal treatment</th>
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<tbody>
<tr>
<td>Depressive disorder</td>
<td>Impairment, Costs</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Fatigue (neurasthenia)</td>
<td>Impairment</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Reported sex abuse</td>
<td>Costs</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Somatisation</td>
<td>Costs &amp; Impairment</td>
<td>Either</td>
</tr>
</tbody>
</table>
Randomised Controlled Trial
Creed et al Gastroenterology 2003 124: 303-317

257 IBS patients.

Psychotherapy (8 sessions) n=85

Antidepressant Paroxetine n=86

Treatment as usual n=86

Baseline

Outcome at
3m
15m
SF36 Physical component score

The University of Manchester

SF36 Physical component score

Start

3 months

15 months

Improvement score

SSRI

Rx as usual

Psychoth.
Improvement in SF36 Physical Component score by reported sexual abuse - scores adjust. for age, gender, deprn & baseline PCS score.

p=0.014, 0.10, 0.98

Creed et al 2003
Conclusion re history of sexual abuse

- Patients with a reported history of sexual abuse do particularly well with psychotherapy (NB small numbers)
- Change mediated by somatisation
- Change also in rectal distension threshold
### Symptoms of the somatization dimension SCL-90.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
<th>Intensity</th>
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</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>0-4</td>
<td>little</td>
</tr>
<tr>
<td>Faintness or dizziness</td>
<td></td>
<td>mod+</td>
</tr>
<tr>
<td>Pains in heart or chest</td>
<td></td>
<td>mod</td>
</tr>
<tr>
<td>Pains in lower back</td>
<td></td>
<td>little q. a bit</td>
</tr>
<tr>
<td>Nausea or upset stomach</td>
<td></td>
<td>q. a bit</td>
</tr>
<tr>
<td>Soreness of muscles</td>
<td></td>
<td>q. a bit mod</td>
</tr>
<tr>
<td>Trouble getting your breath</td>
<td></td>
<td>mod</td>
</tr>
<tr>
<td>Hot or cold spells</td>
<td></td>
<td>mod+</td>
</tr>
<tr>
<td>Numbness or tingling in part of the body</td>
<td></td>
<td>mod</td>
</tr>
<tr>
<td>Lump in your throat</td>
<td></td>
<td>q. a bit</td>
</tr>
<tr>
<td>Feeling weak in parts of your body</td>
<td></td>
<td>q. a bit</td>
</tr>
<tr>
<td>Heavy feeling in your arms or legs</td>
<td></td>
<td>q. a bit</td>
</tr>
</tbody>
</table>
Severe Irritable Bowel Syndrome (n=227)

Chronic fatigue Neurasthenia (n=88)

Somatisation
High number of Symptoms SCL-90 Som (65)

Depressive Disorder (74)

22 23
Prospective population-based study

Screen 2,000 population
11% chronic widespread pain
4% IBS 16% fatigue
76% = syndrome-free

To identify risk factors for symptom persistence
Identify new onset of syndromes
Baseline
12 months
Assess risk factors
Persist
Recover
General Practice Symptoms Study

Francis Creed, Nav Kapur, Chris Dickens, (Psychiatrist)
John McBeth Gary Macfarlane, Alan Silman (Epidemiologists),
Andrew Pickles & Barbara Tomenson (Statistics),
Adrian Wells, (Psychologist)
Jonathan Hill (C & A Psych)
Arthur Barsky (Harvard), Wayne Katon (Seattle)
Funded by UK MRC

- n=1443 population-based sample - all bodily symptoms
Prospective population-based study

Screen population
Free of relevant outcomes
- Chronic widespread pain
- Irritable Bowel Syndrome
- Chronic Fatigue

Assess risk factors

Identify new onset of syndromes

Persist

Chronic widespread pain
Irritable Bowel Syndrome
Chronic Fatigue

Recover

Baseline

12 months

Somatic Symptom Inventory
Multivariate analysis adjusting for all variables

SF 12:
- Physical Comp (p=0.044)
- Mental Comp

No GP visits in prior year (p=0.001)
No GP visits in Follow-up year (p=0.11)

Baseline - 12 months

Somatic Symptom Inventory
Multivariate analysis adjusting for all variables

SF 12:
- Physical Comp: (p=0.044)
- Mental Comp: (p=0.40)

No GP visits in prior year: (p=0.001)
No GP visits in Follow-up year: (p=0.11)

Baseline

12 months

Somatic Symptom Inventory

The University of Manchester
Multivariate analysis adjusting for all variables

- No confidant
- Number of general illnesses
- No consultations year 1
- Whitely
- SSI x Whitely interaction

SF 12 (health status) Questionnaire

No GP visits in previous year (medical records)

Baseline 12 months

Somatic Symptom Inventory
Correlates of Extra-intestinal symptoms

- Extra-intestinal symptoms:
  - headaches, backaches, wheeziness, insomnia, bad breath, fatigue, general stiffness, loss of interest in sex, frequent need to pass urine, dizziness, weakness, sensitivity to heat or cold, palpitations, and tightness or pressure in chest.

Lembo et al Am J Gastro 2009
Mean direct healthcare costs for treatment period (12 weeks), follow-up 1 year and whole trial.

(Creed et al Gastroenterology 2003; 124: 303-317)
Change in SF36 role limitation score by Rx group & depressive disorder (p adj for age, sex, baseline score, pain and other medical conditions) Creed et al 2003

- P = 0.003
- P = 0.76
- P = 0.018
Conclusion re depressive disorder

Patients with depressive disorder:
• Do poorly in treatment as usual group and in psychotherapy group
• Do well with paroxetine

i.e. Rx depressed IBS patients with paroxetine
Patients with Neurasthenia

35% of patients had neurasthenia at start of trial

- This diagnosis predicted a worse outcome
Change in SF36 role limitation score by treatment group – neurasthenia. p adjusted for age, sex, initial score, depression & pain

- neurasth. vs no neur.

Sample sizes:
- 10
- 15
- 20
- 25
- 30

Significance levels:
- p=0.031
- p=0.001
- p=0.058

Treatment groups:
- psychoth.
- paroxetine
- Rx as usual
Conclusion: Psychiatric diagnosis

- Neurasthenia predicts a poor outcome overall
  - Patients with Neurasthenia do better with psychotherapy than with paroxetine.
- Depressive disorder also – poor outcome
- Patients with depressive disorder do better with SSRI antidepressant than psychotherapy
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Monozygotic Mean (95% CI)</th>
<th>Dizygotic Mean (95% CI)</th>
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<tbody>
<tr>
<td>Age</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>gender</td>
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