Pain: science and practice

Amanda C de C Williams

University College London, UK

Pain Management Team UCLH,

International Centre for Health & Human Rights

Definition of pain in humans

"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." *International Association for the Study of Pain 1979*

Because this is subjective, pain is often denied in:

nonverbal children & adults;
people with cognitive impairment or dementia
non-human animals.

"The traditional view that neonates do not feel pain is now being questioned." *Fitzgerald 1989*

It is also denied in those who are judged unreliable in reporting their symptoms: women, people from ethnic minorities, people with little education, people with psychological or psychiatric disorders ….

Science of pain

Melzack & Wall gate control theory 1965 ➡ paradigm change.

Pain is essential: without it, injury often fatal.

From flatworms to humans, aversive response to noxious stimuli, with pain-related learning and context-sensitive pain response.

Tobin & Bargmann *Inc J Neurobiol* 2004

Some animals (vertebrates, some invertebrates) show protective responses, from reflexes to learned avoidance.

Barr et al *Animal Behav* 2008, Dyuizen et al. *J Exp Biol* 2012

In mammals, response is complex, context-sensitive, and often communicative, through posture, movement, vocalisation and facial expression.

Langford et al. *Nature Methods* 2010

Multiple pain mechanisms, all capable of plasticity

Peripheral and central changes in neuronal function, chemical profile, structure, and connectivity.

Spinal and supraspinal systems show central sensitisation: modification in expression of ion channels, neurotransmitters, connectivity (sprouting, reorganisation, crosstalk, recruitment of neurons serving other systems), change in gene expression.

Overall, facilitation of excitation and inhibition is depressed.

Woolf *J Clin Invest* 2010; Woolf & Salter *Science* 2000

As pain becomes chronic, there is functional reorganisation and changes in connectivity: processing of *all* pain shifts to the limbic system. Apkarian et al *Pain* 2005, 2011; Baliki et al *Nature Neurosci* 2012

Animal models of pain rely heavily on peripheral injury or inflammation, and evoked pain. Analgesics that work for those pains often clinically disappointing.

Influences on pain processing *Tracey 2008*

British Journal of Anaesthesia 101 (1): 32–9 (2008)
doi:10.1093/bja/aen102

Physiological & psychological systems that integrate behaviour in pain *Simons, Elman, Borsook 2014*

Neurosci Biobehav Rev. 2014 February ; 0: 61–78.
doi:10.1016/j.neubiorev.2013.12.006.

Brain changes in chronic pain *Kuner & Flor 2017*

Nature Reviews Neuroscience 2017;18
doi:10.1038/nrn.2016.162

This is an integrated plastic system, not a hierarchy

Is chronic pain a disease or an adaptation?

Across diverse aetiologies, the brain of the person with chronic pain shows consistent functional, structural, and molecular changes.

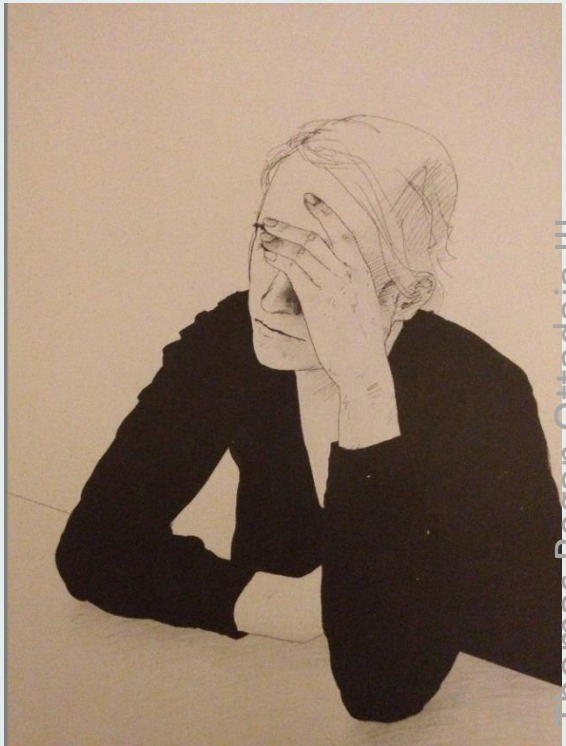
Huge individual differences in connectivity, established over long term (childhood experience) and short term (mood, context).

Chronic pain produces deficits in attention, memory, learning, decision making, risk taking.

These are reversible by pain treatment.

"... is what we see as altered and dysfunctional CNS processing more an adaptive response rather than a disease-like process? *Tracey & Bushnell J Pain 2009*

Where are the explanatory gaps that need psychosomatic mechanisms to fill them?



Thomas Regan Ottadaja III

It is over 50 years since the gate control theory of pain was published by Wall and Melzack ...

... since when, pain science has made huge progress.

"... we are faced with a crisis epidemic of painful states where no peripheral pathology has been discovered or, if apparent, is clearly secondary to some primary change. These conditions now include tension headaches, migraine, temporomandibular joint syndrome, trigeminal neuralgia, the majority of neck and back pains, fibromyalgia, interstitial cystitis, etc.

To add to this problem, it is emerging that, **even where overt pathology** is clearly present, the extent of the peripheral pathology is poorly related to the amount of pain. These conditions include myocardial ischaemia, arthritis, amputation, neuropathies, etc."

Wall 1994

... But dualism is alive and flourishing

"The standard response to this problem [that pain and pathology don't match] is given by the great majority of doctors in two stages.

"First, the normal sensory nervous system is a reliable accurate witness to currently observable peripheral pathology. Second, any deviation from this first rule is a mental aberration. These two rigid rules are simple restatements of Cartesian dualism."

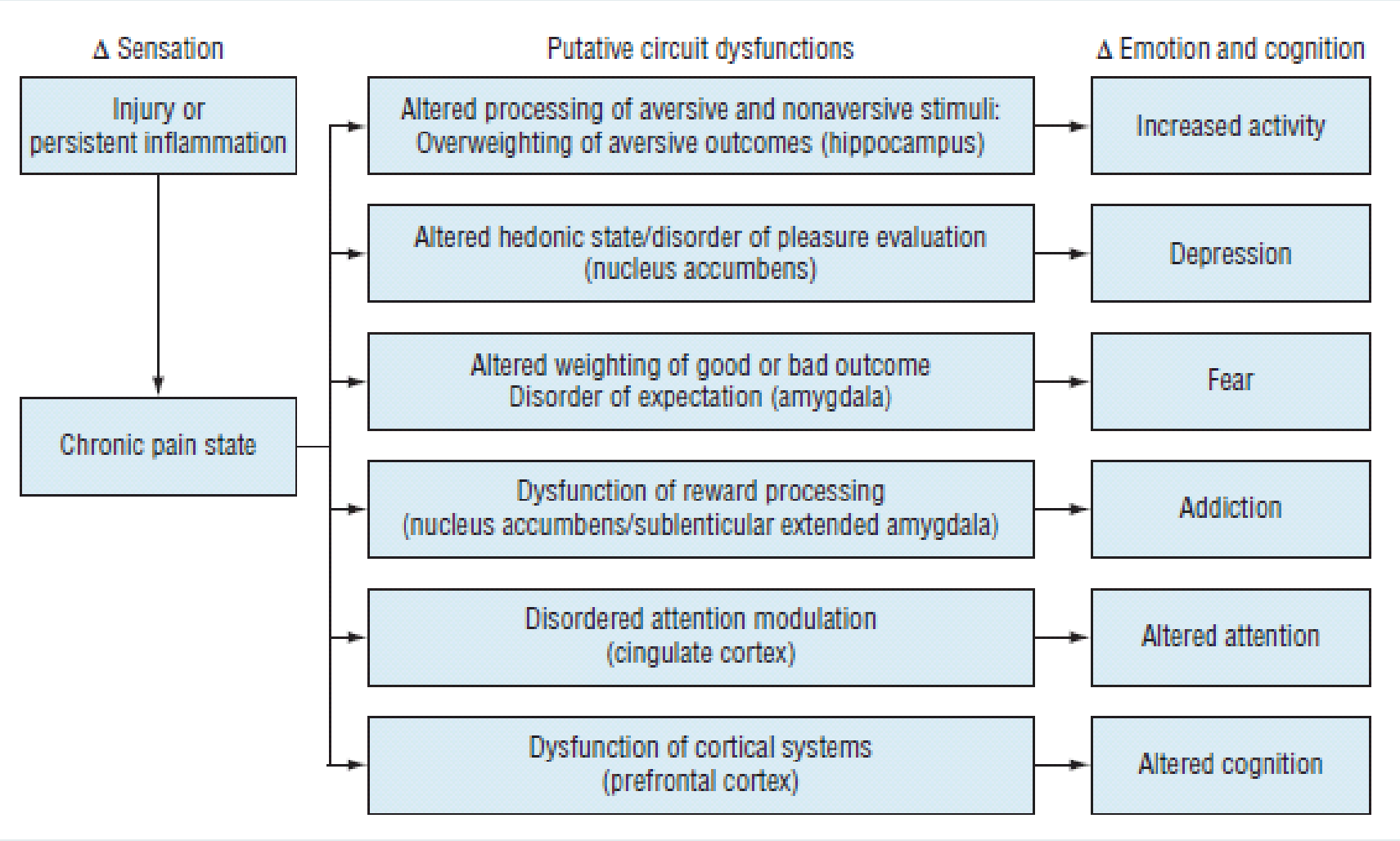
Three better possibilities.

1 we cannot detect all relevant peripheral pathology or change

2 peripheral input can trigger changes in the spinal cord and brain that last long beyond peripheral events have stopped

3 sensory systems are not hardwired but kept stable by dynamic control mechanisms that can be pushed outside their normal working range into an unstable state *Wall, 1994*

Model of pain for psychiatry *Elman, Borsook, Zubieta 2011 Arch Gen Psychiatry*



DSM attempts to classify pain

The definition of pain makes clear that it cannot be denied on absence of identified tissue damage.

Long history of psychological cause used to fill explanatory gap for pain without identified disease process or tissue damage ('somatogenic' pain): *Sullivan MD 2017*

- 'psychogenic' pain (DSM-III 1968)
- 'excessive' pain (DSM-III 1980)
- 'preoccupation' with pain (DSM-IIIR 1987)
- psychological factors in aetiology, exacerbation, maintenance (DSM-IV).

All diagnoses by 'exclusion' of 'sufficient' physical factors.

DSM-5: somatic symptom disorder = symptom > 6 months with excessive thoughts, feelings or behaviours.

ICD-11: chronic primary pain = pain > 3 months associated with significant disability or distress.

If we can see it, it is 'organic' = real.

If we can't see it, it is 'psychosomatic' = ?

Medically unexplained symptoms are 'persistent bodily complaints for which adequate examination does not reveal sufficient explanatory structural or other specified pathology'.

Henningsen et al
Lancet 2007

"Is this some other emotional distress presenting as physical distress?"

Hatcher & Arroll BMJ 2008

"Somatisation ... may result from the use of other defence mechanisms, such as introjection." *Goldberg, Benjamin & Creed 1994*

Doctor assessing should try "matching symptoms to life events"

Bass & May BMJ 2007

But: "Clearly, both neurological and psychiatric disorders involve the brain ... resorting to a model that fails to integrate the mind and body is unhelpful in this area." *Hatcher & Arroll 2008*

"It is wrong to distinguish between real/organic & imaginary/psychogenic [pain], because both organic and psychological factors are often present"

Goldberg, Benjamin & Creed 1987

Medically unexplained symptoms and pain

IAPT Medically unexplained conditions: positive practice guide 2008

"The vast majority of MUPS, such as pain, irritable bowel syndrome, and chronic fatigue syndrome, have no obvious cause and often do not actually require any input from health services."

Commissioning support for London, July 2009

"Consider MUS if symptoms do not fit with findings".

And if

- pain in multiple sites *[osteoarthritis? rheumatoid arthritis?]*
- patient can't give clear or precise description *[visceral pain?]*
- symptoms excessive for pathology
- context of stress
- anxiety about disease or implications of symptoms

Alienating and stigmatising patients

"it has become apparent that the term ***medically unexplained symptoms*** is itself a barrier to improved care". *Creed 2010*

Term/concept is "unacceptable to patients". *Sharpe & Carson 2001*

Study of relative offence to patients of terms: *Stone et al 2002*

label	NNO	what it means to patients
"symptoms all in the mind"	2	mad, putting it on, imagining symptoms
"psychosomatic weakness"	3	mad, putting it on, etc
"medically unexplained weakness"	3	mad, putting it on, etc
"stress-related weakness"	6	proper medical condition
"functional weakness"	9	proper medical condition

They recommend use of the term 'functional' to minimise offence.

Function of pain

Grabs & dominates attention ← reliable sensory system

Prioritises escape ← motor system; rapid response

Promotes recovery & healing ← salience, aversiveness, vigilance

Teaches avoidance in future ← attention and learning

None of these requires that pain intensity signals the extent of tissue damage –

*only that it is sufficiently **salient** and **aversive** to dominate attention and action, and minimise future risk*

Pain motivates: it is a need state, not a sensation

Melzack & Wall 1965

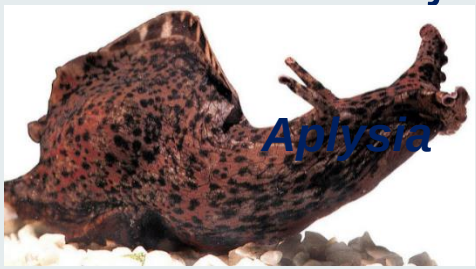
Behaviours associated with pain in animals *Walters 1994*

	function	behaviour
Immediate	Injury detection	*identify location*
		identify severity, change rate
	Withdrawal	*startle type responses*
	Memory	*store context and cue info*
Rapid	Passive defence	*freeze / retreat, protect site, assess risk*
	Active defence	*escape / fight,*
		suppress competing responses
Delayed	Wound protection	*shelter, hide, stay vigilant & immobile*
	Recuperation	*clean & disinfect wound,*
		immobilise injury, conserve energy, monitor healing

Acute pain – or nociception - across animals

There is much debate about whether non-human animals *feel* pain.

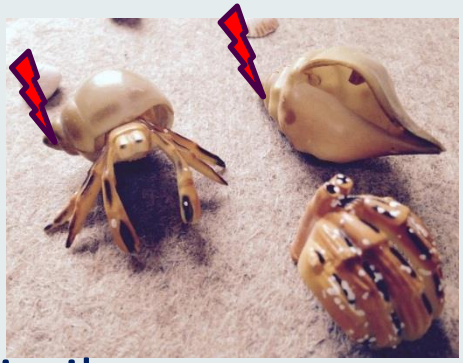
But that's a subjective experience, so is hard to investigate.



Do noxious stimuli produce particular behaviours, and do those behaviours disappear with analgesics or local anaesthetics?

Crook et al. demonstrated that squid with a sensitised amputated stump survive better than squid with blocked sensitisation in stump: first demonstration of the survival value of sensitisation.

Crustaceans show conditioned place avoidance, trade-off between avoiding pain and other reward, guarding of painful limb. *Appel & Elwood 2009*



Studies of pain in insects: similar nociceptors, some similar behaviours *Adamo 2008, Neely et al. 2012*

Pain behaviour in humans in clinical settings

'Pain behaviour' reinforced – rest, social and medical attention, release from unwanted duties, etc. Very limited applicability in clinical settings.

Guarding (slow, restricted movement) is related directly to anxiety not to pain in humans.

Avoidance is variously understood in pain (and other 'MUS'):

- laziness, secondary gain, moral weakness
- overgeneralised learning; fear & overinterpretation of threat

But avoidance is also related to:

- amplified processing especially in limbic system
- failure of extinction of fear
- functional connectivity changes implying reduced descending inhibition

Arif-Rahu & Grap; Intensive & Critical Care Nursing 2010; 26:343-352

Facial expression read across age and ethnicity, modulated by social context, but interpreted using social biases. Scepticism is rife.

Williams *Beh Brain Sci* 2002

Who suffers most from our scepticism about pain?

- Infants and small children
- Women (particularly for pain in reproductive system)
- People with cognitive impairment
- People with mental health problems
- People ethnically or culturally different from ourselves.

Heuristics for discounting / denying others' pain mainly concern oversensitivity, exaggeration for gain, and being unable to express mood or emotions.

These beliefs lead to systematic undertreatment of pain, or no treatment at all, including surgery without anaesthesia.

"… even after successful surgical intervention, victims of torture can continue to complain of pain or report that it has worsened, *despite medical evidence to the contrary*. The patient's complaints … reflect the operation of post-traumatic stress disorder conditions in its complex form."

Wilson, 2004

Culture and symptom presentation

"... somatic presentations of emotional distress are the norm in much of the developing world ... migrants from these countries are likely to describe distress in bodily terms".

NHS Commissioning Support for London 2009

Collectivist societies have more constraints on behaviour and emotional expression, and (adaptively) disclose emotions indirectly, including physical distress. Keyes & Ryff *Soc Sci Med* 2003

International comparison of "somatisation disorder" found no clear pattern:

- somatisation disorder lowest in France & Nigeria, highest in Turkey & Brazil.
- pain persistence highest in Greece and China; lowest in Turkey and Italy.

Controlling for age and sex, populations with lower rates had personal medical system (ongoing relationship, medical records, follow-up).
So somatisation rates may be affected by culture of medical system.

Gureje et al *J Psychosom Res* 2004

Studies of pain using somatisation concept

Review of 116 studies of somatisation (Lipowski definition) in pain published since 1989.

Few defined somatisation: used multiple physical symptoms by self-report.

None met all criteria for somatisation:

- only 4/116 studies checked for pathological findings
- none asked for patients' attribution of their pain
- only 1 study established that patients sought medical care for their symptoms.

Somatisation score based on symptom self-report is overinclusive = symptoms with medical explanation + symptoms that patient attributes to psychological cause + symptoms not brought to dr.

"… the construct of somatisation as applied in pain research is scientifically flawed. Persevering in its misuse will lead only to a poorer understanding of patients with pain ..."

Crombez et al Pain 2009

Chief Medical Officer's Annual Report for 2008 recommendations

"A major initiative to widen access to high-quality pain services would improve the lives of millions of people."

ACTION RECOMMENDED

"A major initiative to widen access to high-quality pain services would improve the lives of millions of people."

- Training in chronic pain should be included in the curricula of all healthcare professionals.
- Consideration should be given to the inclusion of the assessment of pain and its associated disability in the Quality and Outcomes Framework for primary care.
- For patients in hospital, a pain score should become part of the vital signs that are monitored routinely.
- The feasibility of a national network of rapid-access pain clinics providing early assessment and treatment should be explored.
- A model pain service or pathway of care with clear standards should be developed by experts.
- All chronic pain services should supply comprehensive information to a National Pain Database.
- Agencies involved in the management of patients with chronic pain should form local pain networks to work together to improve the quality of local services.
- The Health Survey for England should routinely collect data on the impact of pain on quality of life.

Studies of GP treatment of chronic pain show too much investigation, too little explanation, very little advice, overuse of analgesics and underuse of pain expertise.

- A model pain service or pathway of care with clear standards should be developed by experts.

- Training in chronic pain should be included in the curricula of all healthcare professionals.

… only 14% of people with pain have seen a pain specialist. Systems and infrastructure are not adequate to meet need or demand.

Patients' Association survey of public attitudes to pain, 2010

Largest UK survey: 4.3k respondents, weighted to produce a nationally representative sample, sampled through YouGov.

1.2k had experienced chronic pain.

63% were aware that specialist opinion is a possibility:
23% had been referred for one.

There is one specialist per 32k people with chronic pain.

The Patients' Association recommends:

- development of a patient pathway,
- a commissioning pack,
- good information to make patients aware of treatment options
- education for GPs and others on options for pain management.

How is pain usually managed?

People with chronic pain are offered

- physiotherapy
- psychologically based rehabilitation

} some benefits, low risk

- pharmacotherapy
- sometimes surgery

} some benefits, higher risk

- often, nothing

} increasing disability: recovery rare

What patients are offered depends on
their resources,
their primary care doctors' beliefs,
what is available locally, and other extraneous factors.

They may be segregated by type of pain, or by age, but rarely if ever by their psychological needs.

How is chronic pain treated in primary care?

What predicts consultation with low back pain?

Pain intensity & beliefs about pain for pain of 2-12 weeks; depression & disability for pain >12 weeks. *Waxman et al 1998*

Community survey; half had not consulted in last year.

What does (did?) primary care offer for chronic pain?

Overuse of X-rays; overuse of opioids; divergence from guidelines. This produces no improvement in disability.

Systematic review of standard care arms of RCTs. Somerville et al 2006

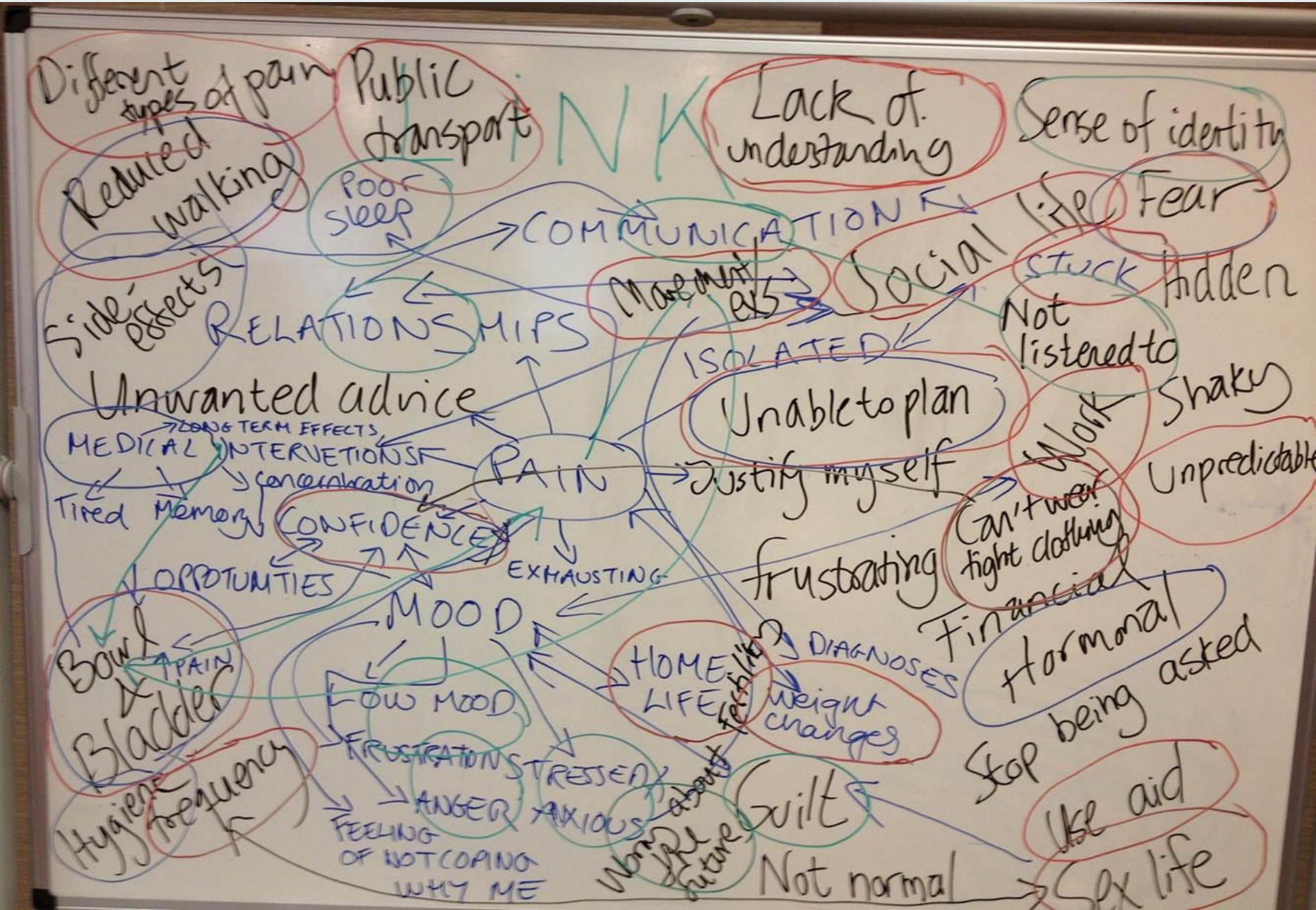
Obstacles to recovery from acute/subacute low back pain: what predicts **persistence**?

Catastrophising & anxiety, **+** belief that back problem will persist, **+** low confidence in ability to function with pain.

Anxiety/depression predicted disability but not persistence.

Need to address beliefs in primary care, not only mood.

Foster et al 2010


Different types of pain
Public transport
LINK
Lack of understanding
Sense of identity
Reduced walking
POOR SLEEP
COMMUNICATION
Fear
Side effects
RELATIONSHIPS
Maternity
Social life
STUCK
Hidden
Not listened to
ISOLATED
Unwanted advice
Unable to plan
Shaky
LONG TERM EFFECTS
MEDICAL INTERVETIONS
PAIN
Work
Unpredictable
Tired
Memory
concentration
Justify myself
CONFIDENCE
Can't wear tight clothing
frustrating
OPPORTUNITIES
EXHAUSTING
Financial
MOOD
Bowel & Bladder
PAIN
HOME LIFE
DIAGNOSES
Hormonal
LOW MOOD
Weight changes
Stop being asked
Hygiene
Frequency
FRUSTRATION
STRESSED
Use aid
ANGER
ANXIOUS
Guilt
FEELING OF NOT COPING
WHY ME
Worry about future
Not normal
Sex life

Aims of (any) pain treatment

Improve control of pain

Help build realistic model of problem

Reduce disabling effects of pain by work towards short and long term goals by graded steps

Reduce distress associated with pain and projected future

Reduce effects of pain on family and friends

Reduce unhelpful encounters with health system

Focus on pain alone may leave patient inactive and anxious.

But focus on distress and activity without trying to relieve pain makes patient feel disbelieved and uncared for.

Psychological factors in pain treatment

Beliefs: unhelpful content, poor understanding of pain

- fearful beliefs about illness and health
- hopelessness about control over illness & health
- pessimism about risks and dangers

Processing: biases & distortions in processing info

- attention: on symptoms & information on risk
- memory: selective for negative info.
- Interpretation in terms of threat = catastrophising

Associated emotions worry, lack of confidence; frustration ….

Behaviours which constitute disability

- avoiding activities associated with pain
- guarded and restricted movement
- contingencies which encourage disability

Best of behavioural models

Fears, risk aversion, avoidance

- well-established fear pathways in brain
- observable behaviours

But many patients don't report fear, and avoid strategically.

Best of cognitive models

Emotional processing of pain (people with chronic pain process even expected experimental pain in emotional areas). *Apkarian et al. 2011*

Biases in information processing: selectively attention to pain and difficulty disengaging from it. *Crombez, Eccleston*

Avoidance / protective behaviours maintained by (mis)beliefs about what's wrong: beliefs underpin behaviours.

Misdirected problem-solving: if pain is problem, no answer; if living with pain is the problem, there are possibilities.

Eccleston & Crombez 2007

Normal processes, not psychopathology or moral failings

SITUATION What are you planning to do?	PREDICTION(S) What exactly do you think will happen? What do you think is the worst that might happen? How would you know if it happened?	EXPERIMENT What can you do to test your prediction? How can you do things differently when you test your prediction?	OUTCOME What actually happened? Was your prediction correct?	WHAT ABOUT YOUR PREDICTION? Did your prediction happen? What have you learnt? Do you have a different prediction now?
Pick up a 3 kg bag of cat litter	*Logic tells me that my spine will be fine. BUT I can't help feeling that my spine will crack and a disc bulge out and I'll have excruciating pain and be laid up for days*	*Pick up the litter in COPE – where the physios will be, just in case.* *I can use my breathing skills to relax*	*I picked it up! My back didn't hurt half as much as I thought it would. It felt stiff, but that's to be expected*	*No it didn't!!* *I've learnt that I can pick up 3kgs without damaging my back. My back is stronger than I thought.* *Next time I'll feel stiff but my back can tolerate picking up 3kgs*

Psychological intervention: changing the individual's relationship to pain

Information, education, access to information

Distinguishing what can and can't be changed: generating hope, setting goals and timescales.

Breaking down goals into manageable steps and identifying what those need to work.

Problem-solving around obstacles to making those changes.

Identifying thoughts and thinking patterns which are unhelpful / unproductive, and learning to challenge them, or disengage.

… All those are taught as self-management for the longer term, though not all people master them.

Delivered by a well integrated team of doctor, physiotherapist, psychologist, nurse … + OT + others as needed

Systematic reviews & meta-analyses

authors	date	RCTs	N	pain site	improved
Turner	1996	4	>200	low back	multiple
Williams et al	2012	42	>4800	mixed	multiple
Van Tulder et al	2000	7	>300	low back	pain, function
Kamper et al	2014	41	>6800	low back	pain & function
Nestoriuc et al	2008	21	>3000	headache	headache freq.
Glombiewski et al	2010	23	>1300	fibromyalgia	multiple
Pike et al.	2016	13	<500	mixed	healthcare use

Conclusion: small but consistent benefits; it would take a large number of negative trials to overturn these findings

Summary of CBT for chronic pain, Cochrane review 2012

Small to moderate benefits over no treatment, more for disability, mood and catastrophic thinking than for pain.

Some gains lasted six months or more.

Results are as good /disappointing as other available treatments: medication, surgery, physiotherapy.

Actual clinical treatment may be better than trials:

- clinicians more skilled and experienced
- treatments not so brief
- treatment more personalised

Challenge now is maintaining gains and building on them: important role for technology.

Can we individualise treatment better?

Subgroup by diagnosis? By pain site? By psychological variables?

Letting patient choose? No empirical support.

"Predictors" rarely hold up across trials, or even within them.

Responder analyses: but many processes are "polymorphic".

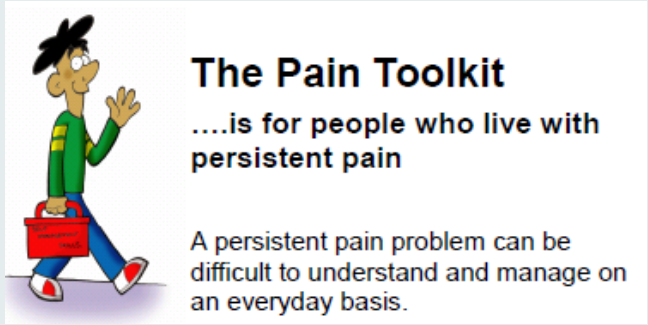
N = 1 trials: theory-driven, systematic treatment with one component at a time, switching orders across patients.

Process of change: routine in-session monitoring to identify trajectory of change & adjust treatment accordingly.

Or opt for "self-management": generalised instruction

Advantages of books & internet

- easily accessible as needed
- more informal than treatment
- easily translated into other languages



Efficacy disappointing & high dropout *Bender et al 2011*