A Sad State of Affairs: A Review of All Current Treatments for Non-malignant Chronic Pain without Sufficient Explanatory Pathology

This purpose of this paper is to assist health professionals, in collaboration with their clients, to make more informed decisions in relation to treatment of non-malignant chronic pain without sufficient explanatory pathology.

Declaration of Own Work

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Highlights

- We demonstrate that there is no current treatment for non-malignant chronic pain without explanatory pathology which can be described as efficacious, including the newer "comprehensive" programs.
- We provide a strong rationale for the failure of current treatments.
- We propose the testing of a novel but well-supported treatment for non-malignant chronic pain without explanatory pathology which may prove to be significantly more successful that current treatments.

ABSTRACT

To date it appears that there has been no comprehensive aggregated analysis of the efficacy of the very wide range of treatments currently utilised for non-malignant chronic pain without sufficient explanatory pathology.

The purpose of this literature review was to investigate evidence for and against the widest range of pharmacological, physical/mechanical, and psychological treatments currently in use by health professionals.

As such we reviewed evidence for pharmacotherapy, physical therapy, surgery, chiropractic, acupuncture, TENS, or psychological therapies such as cognitive behaviour therapy (CBT), EMDR, mindfulness, and the newer multi-disciplinary/comprehensive approaches with respect to efficiency, efficacy, effect sizes, and cost. Although readers may already realise that some of these are not efficacious and can be regarded as pseudoscientific, we felt it was important to include them in this review because they continue to be used and promoted by front-line health professionals.

We found that without exception, all studies of all treatments in current use demonstrate minimal to no effectiveness in reducing reported pain levels, and demonstrate only marginal effectiveness (and often no effectiveness) in reducing comorbidity or increasing quality of life.

Finally we initiated review of evidence for a new paradigm in the understanding of non-malignant chronic pain without sufficient explanatory pathology which both explains the failure rate of current treatment, and points clearly to an entirely new direction of therapy.

THE PROBLEM OF CHRONIC PAIN

There isn't currently a definitive analysis of the entire global economic burden of chronic pain, but this burden is likely to be well be over a trillion dollars annually, with the USA alone accounting for up to $635 billion[1]. Prevalence and costs are increasing and the World Health Organization predicts that by 2030 chronic pain will be a significant co-morbidity in the four biggest disease burdens globally[2].

According to Safe Work Australia, in the workers compensation space the cost of chronic pain has more than doubled in the last 11 years[3].

In Pain Australia's 2018-19 Pre-Budget Submission[4] a claim is made that the failure to relieve chronic pain is due to the "fragmentation" of chronic pain services, followed by a recommendation of increased access to allied health services and greater communication between service providers[5] as a comprehensive, multi-disciplinary approach to chronic pain.

However to date we do not have robust evidence for significant efficacy of any current treatment for chronic pain, and medical practitioners in NSW are advised to inform their patients that there is not yet a cure, but that management of the pain is the goal of treatment, such that quality of life is maximised despite the pain (https://www.health.nsw.gov.au/pharmaceutical/doctors/Pages/chronic-pain-medical-practitioners.aspx).

So merely increasing access to current services, and having service providers share client information more comprehensively, may be a recipe for dramatic increase of costs without significant benefit, despite claims to the contrary. We will expand on this point later in this paper.

While there have been claims of efficacy for pharmacological interventions, physical therapies, cognitive behaviour therapy (CBT), EMDR and mindfulness in the treatment or management of chronic pain, it is widely recognised that both effect sizes and efficacy rates are low (or even no different to placebo), and despite small improvement to quality of life scores sometimes being reported, there is little or no change in pain scores. This is frequently the same for TENS and even for surgical intervention, as will be shown in this paper.

Current research relating to chronic pain has been restricted to the above treatments which we already know do not have significant clinical effectiveness, and these are variants of cognitive behaviour therapy, physical therapy, new pharmacological strategies, and even acupuncture though it is widely recognised and will be demonstrated below that acupuncture is no more than expensive and relatively risky "theatre" with effects no different to placebo. Many studies show that surgical intervention produces results no better than sham surgery, and that the TENS machine is also problematic, with one meta-analysis reporting that 15 out of 17 trials showed it to be no better than placebo[6].

The development of a truly efficacious treatment for non-malignant chronic pain without sufficient explanatory pathology would not only bring relief to over a billion sufferers, but would relieve a burden of cost that is currently endangering our health system and harming sufferers and their families.

This paper seeks to give robust evidence that current treatments, being the three strands of standard treatment strategies for chronic pain (pharmacological, physical/surgical, and psychological) are not achieving significant benefit for any stakeholder including the sufferer. In the interests of fully explaining why current treatments are so inefficacious we also begin to set out a more useful understanding of etiology for the majority of non-malignant chronic pain and chronic pain symptomatology, which critically points to a new direction of treatment.

Etiology and Nature of Chronic Pain

Prevalence and Cost

Non-malignant chronic pain affects 1 in 5 adults and as many as 1 in 4 children. Almost 50% of cancer patients continue to experience chronic pain after remission. The global cost burden is difficult to calculate and may be trillions of dollars annually. The latest Deloitte report[7], released in January 2019, put a figure of $139 billion per annum in Australia alone on direct costs only, not counting loss of income to families and communities, damage to productivity in the workplace, loss of human resources in the community and families, and of course the horror of human agony that some 4.5 million Australian chronic pain sufferers (over 1.5 billion globally) are struggling with, along with their families and loved ones, at any given time. Nevertheless this modest and incomplete estimate of total costs translates to over $30,000 for each and every sufferer.

One of the most accurate types of records in relation to chronic pain is kept by workers compensation stakeholders because after all that is their bottom line. According to the latest report by Safe Work Australia[3], over the last 15 years, despite decreased incidents of injury, compensation pay-outs have more than doubled. For low back pain alone (the single most common and most expensive injury and the most common of all chronic pain), workers compensation pay-outs are approximately $8 billion per annum in Australia.

The National RTW Survey[8] shows that the percentage of people returning to work after injury is decreasing and in 2018 was at a low of 50-80% dependent upon jurisdiction. Even this figure is not as optimistic as it might first appear, because amongst those who reported returning to work, approximately 20% had had to take further time off due to persistent pain. In addition a large percentage of people reported returning to work while still in pain, not being able to return to role, and not being able to work full-time.

Table 1 – Total Costs Associated with Chronic Pain in Australia, 2018

Cost Component	Total Cost ($bn)	Per Person ($)	Proportion of Total (%)
Health System	12.23	3.771	8.8
Reduced Employment	36.18	11,161	26.0
Absenteeism	3.17	979	2.3
Presenteeism	8.99	2,773	6.5
Informal Care	4.51	1,390	3.2
Aids & Modifications	0.57	176	0.4
Deadweight Losses	7.58	2,338	5.4

Total Financial Costs	73.22	22,588	52.6
Loss of Wellbeing (Non-financial)	66.10	20.391	47.4
Total Costs	139.33	42.979	100.0

Source: Deloitte Access Economics Analysis[5]

Notes on the above table:

Loss of wellbeing was calculated in terms of DALYs (Disability Adjusted Life Years - The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability, using verified VSLY (Value of Statistical Life Year due to medical intervention).

Deadweight Losses consist of the loss of consumer and producer surplus, as a result of the imposition of a distortion to the equilibrium (society preferred) level of output and prices. In this case they include welfare payments, Commonwealth health expenditure, lost consumer taxes, lost company taxes, and lost carer taxes.

In this paper we make the claim that the primary reason that current costs are so high is that current treatments are not working, and this is borne out by the data held by workers compensation companies, who can see from their records that their clients with chronic pain are not generally getting better (interview with Chairman of PSC Insurance Group, August 2019). So perplexed are they that so many billions of dollars are being spent on so much treatment, that some in the industry have formed the firm opinion that significant cost is due to "cheats and malingerers", rather than understanding that the treatments at their disposal are ineffective, or that clients have given up and are just doing their best to survive an impossible situation.

In regard to lack of efficacy of current treatments, we see similar data in the health funds, in hospital admissions, and in the disability sector where chronic pain has become disabling. Health fund pay-outs for chronic pain treatment in Australia sit at some $12.23 billion per annum and are increasing. This is recognised as being unsustainable. No nation can maintain a workable health system under that kind of financial duress.

In order to bring relief to those who suffer, and put an end to the financial bleeding in all sectors - family, community, workplaces, the health system and the nation - we need a better understanding of the nature of chronic pain, and a better treatment approach with much higher efficacy and effect sizes, which is also more efficient and cost-effective to provide.

This is the rationale for a new framework which this paper expands upon. We:

- Examine the evidence for lack of efficacy of current treatment strategies for chronic pain
- Provide verified evidence for a new theory of non-malignant chronic pain, which explains precisely why current treatments are so ineffective, which will form the basis for a consequent paper
- Provide evidence for a new direction of therapy for non-malignant chronic pain, which is planned to include a phase 3 clinical trial in 2020

How Does Chronic Pain Arise

For the purpose of this paper we are specifically referring to non-malignant chronic pain without adequate explanatory pathology. This includes most back pain, shoulder pain, neck pain, post-injury pain, post-surgical pain, post-disease or post-infection pain, phantom pain, "nerve" pain, fibromyalgia, and other "mystery" pains.

This paper is not relevant to types of pain that are labelled "chronic" but which are acute in nature, such as endometriosis, adenomyosis, some of the myalgias (eg polymyalgia rheumatica) and rheumatic conditions generally, as well as pain from cancer.

The table below sets out causes of chronic pain in Australia for 2018, courtesy of the 2019 Deloitte report, The Cost of Pain in Australia[7].

Table 2 – Causes of Chronic Pain in Australia - 2018

Condition	**Proportion of chronic pain due to condition (%)**	**Prevalence**
Injury	38.0	1,231,865
Cancer	1.6	51,868
Musculoskeletal	24.1	779,896
Mental health/behavioural	1.1	36,274
Gastrointestinal	1.0	33,251
Neurological	0.7	21,160
Infection	0.6	18,137
Circulatory (cardiovascular)	0.7	21,160
Genitourinary	0.6	18,137
Endocrine/hormonal	0.2	6,046
Respiratory	0.2	6,046
No clear reason/don't know	31.4	1,017,910
Total	**100.0**	**3,241,750**

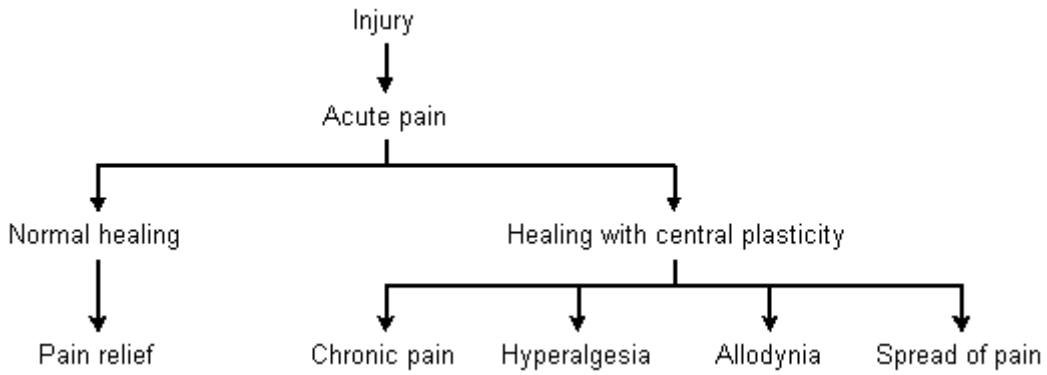
Source: Deloitte Access Economics[7]

It can be seen from the above table that 93.5% of chronic pain presentations are comprised of post-injury, musculoskeletal, or nil pathology. This overwhelming majority of chronic pain presentations is where we intend to show that current treatments have low or no efficacy, and that we therefore need to take a different approach.

Without exception most types of chronic pain begin as some kind of acute episode whether injury, surgery, disease, trauma, or some other insult. However the great majority of people who suffer acute pain (or an acute episode) from a whole gamut of causes, go on to fully heal, the pain fades away, and they return to normal roles. For example when most people experience back pain, provided they remain sufficiently mobile their back pain will naturally fade away very quickly, generally within 2 weeks[9].

In contrast, some 1 in 5 people heal in exactly the same way but the pain does not fade away. Instead it can remain as is, become worse, generalise to other areas, become quite bizarre (for example a feather touch can feel like a severe burn, or there can be sensations like electrical shocks, or flowing water), or even involve other symptoms such as swelling, inflammation, sleep dysfunction, digestive dysfunction, and in fact dysfunction of almost any function governed by the central or autonomic nervous systems.

Figure 1 – Pathogenesis of Chronic Pain[10]



Source: Marcus, DA, Treatment of non-malignant chronic pain. American Family Physician. 2000 Mar 1;61(5):1331-8, 1345-6.

This behaviour of chronic pain is what differentiates it from acute pain, even at a surface assessment. Acute pain is nociceptive, meaning that it is experienced as a result of receptors that are sensitive to mechanical, chemical, or temperature signals and which report detection of abnormal or harmful activity.

While some researchers posit an "over sensitisation" of nerve pathways as a mechanism for chronic pain[11] or implicate inflammation as a causative factor[12], others have provided strong evidence of a genetic component. Johnston et al[13] recently carried out the largest genetic survey of chronic pain patients to date, 380,000 Britons, and identified 76 genes that they describe as independent risk factors for complex chronic pain. Many of these genes were associated with heightened somatic sensing, and others with anxiety and depression.

Baliki[14] has demonstrated via fMRI that chronic pain and acute pain involve very different brain activity, with chronic pain appearing to be very similar to emotional activity mediated via the amygdala, "implying that the sensory, emotional, and cognitive properties of spontaneous pain of chronic pain are very different from acute pain".

Many researchers now say that chronic pain is "in the brain"[15–17], and in an effort to treat this "brain problem" have recommended psychological treatments such as CBT and mindfulness, which as can be seen below in this paper have minimal if any success rates, similar to placebo (with the definition of "placebo" being "false attribution", "regression to the mean", "delusion", or "error of judgement").

As a society we desperately need a better understanding of what chronic pain actually is, and we urgently need treatments that do actually work in a much more significant way for the majority of sufferers, and which present the lowest risk possible.

The Three Standard Treatment Types for Chronic Pain – An Overview

The three standard treatment types for chronic pain in Australia are: pharmacological, physical (including physiotherapy and surgery) and psychological.

According to a study by Williams et al[18] doctors primarily prescribe medication with only 18% given advice about the importance of remaining active, with 57% of patients prescribed anti-inflammatories, 20% prescribed simple analgesics.

According to Dennis et al[19] some 7% of chronic pain clients are referred to physical therapy, or recommended to use TENS, acupuncture, or chiropractic, and as a last resort surgery.

Only around 1.2% of patients are referred to a psychologist for treatment with CBT or mindfulness or other psychological intervention, according to the Australian Institute of Health and Welfare (https://www.aihw.gov.au/getmedia/179996b8-b9c4-4c78-9b86-cfb419347a1e/gpaa99-00-c03.pdf.aspx).

The following sections will show that none of these interventions are having any significant effect on most people's suffering, will attempt to explain why that is so, and will also attempt to provide an accurate cost of the financial waste of prescribing treatments which are unlikely to have any significant clinical effect.

Pharmaceutical Strategies

Pharmacotherapy for chronic pain does have some scientific evidence, even though most physicians agree it is far from satisfactory, and to date we have no medication that clinical trials have demonstrated can help most people[20]. In fact we can see that for pharmaceuticals the percentage of people who achieve even 50% reduction in their pain, can be as low as 4.5%[21] in the case of fibromyalgia.

Averaging out NNT (number needed to treat), according to a 2015 report published by the West Australian Department of Health[21] only 17.89% of people suffering from neuropathic pain achieve 50% or more reduction in their pain.

Supplementation with "natural" drugs has proven to be even less effective. Some studies show that that as few as 2% of chronic pain patients achieve less than 20% pain reduction[22] when prescribed alternative medication, which could be entirely due to placebo (false attribution, regression to the mean, or simple delusion/error of judgement).

The latest Deloitte report[7], released in January 2019, shows that in Australia we spend over $652 million per annum on medications for chronic pain, not including several of the newer opioids, cannabinoids, low-dose naltrexone, PEA, or other prescribed medications. Given that a clear majority of people are not being helped by their medication, this represents a massive waste and it is critical, for humane reasons as well as for cost savings, that we find a far better way to help these people to eliminate or greatly reduce their suffering.

It is difficult to determine what is being spent on CAM (complementary alternative medicine) in Australia, but the RACGP's research shows that we spend more on CAM than we do on the Pharmaceutical Benefits Scheme[23] – for nil discernible benefit.

Nevertheless, despite the low efficacy and massive cost, it is possible that pharmacology can play a vital role in pain control for some people, and many doctors and pain specialists will trial a number of medications in order to try to find one or a combination which works for an individual patient.

All drugs have side effects, and different people, and different types of pain, respond differently to different preparations or combinations. This is why it can be challenging for doctors and pain specialists to try to achieve a medication mix that seems to get a result for each particular patient, without burdening them with damaging or unpleasant side effects.

Some medications, such as low-dose naltrexone, medical cannabis, and PEA, are beginning to be prescribed for chronic pain, unfortunately because of public pressure due to anecdotes being shared on social media, but which do not have any robust research to support them.

A range of medications, including those less commonly prescribed, are described below, along with evidence for their limited efficacy.

Paracetamol

Paracetamol (acetaminophen) does not require a prescription and is a simple analgesic that may be popular as a first choice for chronic pain because it is a "NSAID sparer", meaning that it can avoid the known side effects of nonsteroidal anti-inflammatories.

While many people will be familiar with this drug because it is part of the family medicine cabinet, and use it successfully for headache, toothache, and other mild-to-moderate acute pain, it has not been shown to be superior to placebo for non-malignant chronic pain without sufficient explanatory pathology.

Cochrane reviews are considered to be more rigorous than other systematic reviews or meta-analyses, and also generally more up to date. A 2017 Cochrane review by Cooper et al[24] found that there was no evidence at all for any efficacy level of paracetamol for chronic pain of any kind.

Andrew Moore, Honorary Senior Research Fellow at the University of Oxford, agrees that we don't have evidence for efficacy of paracetamol for chronic pain and that liver damage is possible for some people even in normal, low doses. He says, "The evidence is that it probably does not work at all for chronic pain. Large, good and independent clinical trials and reviews from the Cochrane Library show paracetamol to be no better than placebo for chronic back pain or arthritis. This is at the maximum daily dose in trials lasting for three months, so it has been pretty thoroughly tested."

It should be noted here that the word "placebo" as used in clinical research is an umbrella term covering regression to the mean, false attribution, error of judgement or plain delusion.

Antidepressants

As well as depression being a reasonable outcome of the long-term burden of pain, there is considerable evidence that people with depression feel pain more acutely, and depression is regarded as the most common comorbidity of chronic pain[25]. As well as targeting depression, the theory is that antidepressants can also decrease the incoming signals from the spinal cord to

the brain and improve pain relief[15]. They tend to be used only where nerve damage has inactivated receptors that narcotics could target (eg in cases of shingles, which is chronic pain which has an acute cause and therefore cannot be regarded as non-malignant chronic pain without explanatory pathology in any case).

While some research indicates positive effect on pain levels[26], others indicate nil or nil compared to placebo, with confounding factors being open label research, inconsistency of dosages used, and even no control or placebo[27].

In addition all antidepressants carry a risk of side effects and some (such as Cymbalta) are notorious for severe side effects and carry a long list of drug incompatibilities (https://www.mayoclinic.org/drugs-supplements/duloxetine-oral-route/side-effects/drg-20067247?p=1).

A systematic review and meta-analysis by Riediger et al[28] found that while low-dose antidepressants generally had good tolerability, "Drowsiness, constipation, and dry mouth were the most frequent adverse effects. Less often, headache, palpitations, and irritability as well as blurred vision were reported".

Anti-inflammatories

There are not yet any completely safe anti-inflammatory medications. This does not mean that they should not be used because of fears of addiction, dependency or side effects. With help from the supervising doctor, a treatment can be found that as much as possible minimises these risks at the same time as maximising comfort and wellbeing, which is the main objective.

There are a range of pharmaceuticals which qualify as anti-inflammatory and most of these are descendants of aspirin, which has risks relating to bleeding because of its blood thinning properties. These drugs are also notorious for causing gastrointestinal problems.

The COX-2 inhibitors are a class of drugs (NSAIDs -nonsteroidal anti-inflammatory drugs) which selectively inhibit COX-2, an enzyme involved in the inflammation pathway, while sparing COX-1 and as a consequence reducing gastrointestinal toxicity. Vioxx was an example of a COX-2 inhibitor which was withdrawn from the market after reports of associated heart attacks, strokes and blood clotting[29].

Perhaps rather bizarrely, a systematic review and meta-analysis by Machado[29] concludes that NSAIDs are effective for spinal pain, but at the same time states they are no better than paracetamol, (which in an above section we see is not better than placebo). Machado states, "At present, there are no simple analgesics that provide clinically important effects for spinal pain over placebo."

It is difficult to reconcile Machado's claim for efficacy with his clear statements of inefficacy. As is common in papers which claim statistical significance for one treatment or another for chronic pain, this does not in any case necessarily translate to clinical significance for the sufferer[30], and claiming both efficacy and inefficacy around the same outcomes makes no sense.

The failure of anti-inflammatory medications of all kinds (including the gabanoids which are anti-epileptic medications with an anti-inflammatory action) indicates that inflammation, while a popular target in the treatment of chronic pain, is not necessarily a significant cause.

Narcotics - Opioids

Narcotics work by acting on the central nervous system itself. A drug which is effective as a narcotic always has unwanted side effects, for example constipation and respiratory depression, as well as risk of addiction if not carefully managed.

When pain doesn't respond to one of the aspirin-like drugs, it's common to combine those with a weak narcotic. The aim is to optimise the desired effect and minimise the risks.
So in an effort to eliminate or decrease suffering, opioids have been a last resort, but are nevertheless a common prescription when nothing else seems to help. This has been problematic because there is strong evidence that opioids decrease in effectiveness over time, but simultaneously cause higher sensitivity to pain and a worse pain experience. It's common for patients withdrawing from opioid medication to report lower pain levels[31,32,33].

It is widely recognised that we have a problem with opioid addiction and overuse, and this has led to changed rules and guidelines around prescribing practices, with many doctors reported to be afraid of losing their licence to practice if they prescribe to the level their patients require, or even if they prescribe opioids at all. So while we can see that many people who are skilfully managed away from opioids and onto other treatments are better off, we can also see patients being suddenly cut off from the only medication they believe gives them any hope, and without an appropriate alternative. Increased hospitalisation when pain becomes unbearable, and increased suicide rates amongst chronic pain patients, have been the outcomes of this sudden change in prescribing practice[34].

A further potential complication has come to light in a recent study of over 25,000 military veterans, which found that people who took prescribed opioids for chronic pain were at significantly higher risk for pneumonia[35]. It has been suggested that opioids like morphine may actually suppress the immune system[36].

In addition to this, according to the latest Deloitte report[7] the direct hospital cost of prescription opioid misuse is around $13.4 million per annum, and in the year 2015-16 there were 784 deaths from prescription opioid misuse amongst chronic pain patients.

There is considerable evidence that opioids can be useful in the short term for acute pain, but many experts claim there is no robust evidence that opioids are any better than paracetamol for non-malignant chronic pain without sufficient explanatory pathology[37] and that paracetamol is not effective for chronic pain in any case[24] (see above).

A Cochrane review by Noble et al[38] found that although some specific patients may experience long-term relief from opioid medication for chronic pain, the evidence for that was both weak and minimal, and that in most cases there was lack of evidence for efficacy.

Narcotics - Medical Cannabis

We have been unable to identify robust, quality studies which show that medical cannabis significantly helps with chronic pain. Some studies suggest it can cause increased pain[23, 26, 27, 28].

A systematic review and meta-analysis by De Vita et al[39] of 18 separate studies showed that while cannabis could raise the pain threshold minimally prior to being given a painful stimulus, it had no effect at all on the intensity of pain, nor did it reduce perceived unpleasantness of pain, and there was no reduction of mechanical hyperalgesia.

A meta-analysis by Hill et al[40], while referring to reduced opioid use and other benefits when cannabinoids were used as an opioid alternative, also refers to increased pain levels for some users.

An Australian study by Campbell et al[41] is one of the largest and longest to date. Researchers at the UNSW Sydney examined the effect of cannabis on 1500 Australians who were already part of research on treating pain through prescription opioids.

This study found that non-cancer pain sufferers who used available street-market cannabis had higher pain levels than those who did not use cannabis. Strangely, although 70% of the participants claimed that the cannabis helped, researchers reported: "At each assessment, participants who were using cannabis reported greater pain and anxiety, were coping less well with their pain, and reported that pain was interfering more in their life, compared to those not using cannabis". The study found no evidence of reduction of opioid use in individuals using cannabis.

Another study by Wallace, et al[42], although on healthy volunteers, demonstrated that cannabis could seemingly both increase or decrease pain. From this study we can understand that although many people report lowered pain levels with the use of cannabinoids, it is quite clear that cannabinoids can also make pain worse, and that the dosage patterns are not linear – it's not simply a matter of more is better, and it's not even that researchers have been able to identify a "sweet spot". Also we can see from the Campbell[41] study that subjective reports of less pain do not necessary match up with VAS estimates offered by the participants themselves. In other words, people make claims about pain relief that they themselves then contradict.

Another way of looking at this study is that the outcomes were random and not correlated with use of cannabis.

Nevertheless the hype around cannabis continues to drive research efforts, and we continue to see poorly designed trials attempting to show that cannabis can significantly help chronic pain, but which do no such thing. A good example is one just published in the Journal of Clinical Medicine (2019) by Sagy et al[43] which states as a conclusion "… cannabis could be a promising therapeutic option" for fibromyalgia.

However the authors themselves describe the serious limitations of the trial: "Our study has several important limitations. First, this study was of an observational nature and could not establish causality between medical cannabis use and improvement in fibromyalgia outcomes. ... Second, the close to 30% non-respondent rate in the six months follow-up may have resulted in a non-response bias. ... Third, the fibromyalgia diagnosis was established by the referring

rheumatologist; therefore, we could not verify that the American College of Rheumatology preliminary diagnostic criteria for fibromyalgia were fulfilled in every case. Fourth, we had no control group to compare the clinical outcomes of medical cannabis use. ... Fifth, the change in the utilization of other drugs (than cannabis) for the treatment of fibromyalgia was based on self-reports and was prone to recall biases."

So in this study self-reported medications such as opioids and benzodiazepines were also being used, there was no placebo control or indeed any control, there was no way to accurately measure any drug being used by any participant, and the diagnosis of fibromyalgia was not properly established in the first place. This trial was so confounded that no conclusions can be inferred and the offered conclusion of "promising therapeutic option" is completely unsubstantiated.

At this time we simply do not have enough evidence for medical cannabis in relation to chronic pain to make any recommendations for its use because even though we have *some* potential evidence for improvement of chronic pain, nausea and seizures for example, this must be weighed against the fact that cannabis can also make pain, nausea and seizures even worse[32,33].

Naltrexone

Naltrexone is an opioid antagonist, meaning that it blocks the effects of opioids.

There are some keen fans of LDN (low-dose Naltrexone) in both the medical profession and the general public, but despite many claims of effectiveness there is not any definitive, robust research that demonstrates benefit for chronic pain, nor which largely precludes some very unpleasant side effects.

We have been unable to identify a single valid study which demonstrates significant effectiveness for any health issue outside of addiction studies.

Some chronic pain studies do show benefit but are so confounded they cannot be used for meaningful analysis. For example a 2018 study by Parkitny[46] is typical of what is found in a scholarly search for LDN and chronic pain, and primarily focuses on fibromyalgia. There was no control at all, let alone an appropriate placebo control, the study was underpowered with only 8 participants whose diagnoses were not confirmed but who were referred by a rheumatologist. (Note that it may be inappropriate for a rheumatologist to diagnose fibromyalgia in any case, because fibromyalgia is no longer considered to be an immune disorder. Canada has proscriptions in place against rheumatologists being involved in treating fibromyalgia as it now regarded to be outside their scope of practice[47].) Despite all of the flaws in this study there was a reported change to the VAS (visual analogue scale used to subjectively assess pain level out of 10) of only 1.5 points, easily attributable to placebo (false attribution, regression to the mean, or delusion/error of judgement), and the LDN had no effect on the inflammation markers detected in some of the participants, with no correlation between inflammation markers and reported pain.

Certainly, as with many medications and treatments, LDN can "seem" to work, but some patients also describe frightening side effects. This, together with the complete lack of robust evidence, explains why so many doctors are not keen to prescribe LDN for chronic pain at this time.

Anti-epileptics

These include the gabanoids and are also known as anti-seizure or anti-convulsant medications.

During an epileptic fit groups of nerve cells in the cerebral cortex become very excitable and fire in harmony. Anti-epileptic drugs prevent this simultaneous firing. In some pain, for example trigeminal neuralgia (which although labelled chronic is acute in nature), it is thought that cells in the brainstem which receive sensory nerves from the face, fire in unison, causing a stab of pain.

There is moderate- to high-quality evidence that anticonvulsants are ineffective for treatment of low back pain or lumbar radicular pain. There is high-quality evidence that gabanoids (Lyrica is one commonly prescribed) have a higher risk for adverse events[48] and yet have an NNT (number needed to treat in order to achieve at least 50% of pain relief for one patient) of 5[21]. A report published by the West Australian Health Department[21] lists a NNT for neuropathic pain ranging from 7.2 to 22.

PEA

PEA is the fatty acid palmitoylethanolamide and is considered by many to be "natural". It is experiencing a rise in reputation on social media at the moment, partly on the basis that it occurs naturally in the human body and plays a role in countering inflammation, but mostly on the basis of completely unvalidated anecdotal reporting and fringe site promoting or selling supplements.

PEA could theoretically be useful in cases where inflammation is the cause of chronic pain (ie, not merely coincidental to the pain), which is most likely the minority, and explains why PEA is generally not helpful to most chronic pain patients. And we have not yet seen that inflammation is generally or commonly correlated with chronic pain in any case.

One recent, high-quality, negative study recently showed no benefit over placebo[49].

Two positive studies examined were either uncontrolled or not blinded or double-blinded.

This isn't exciting, especially given that PEA is very expensive and has to be compounded by a specialist pharmacy.

Yet another positive study was not a research study at all, but a case series where PEA was plainly given as an additional treatment. Since we know we will almost always see improvement where "something else" is done *in addition* to existing treatment, this is also a highly questionable study. It is common in studies of CAM therapies to add a known ineffective CAM treatment to an effective treatment and then claim that the CAM therapy was the cause of any improvement.

As I tried to find controlled, randomised, double-blind trials, even where these were referred to as such in articles and other papers, and cited fully in the references in lists claiming to have those features, I found that they did not. It was common for a trial to be described as controlled, randomised, and double-blind, but on reading to find that it was just a very small case series, no better than a collection of anecdotes.

As I looked more widely to try to find evidence for PEA, I consistently came across repeated citations of these same studies that are quite flawed, as well as animal studies that usually do not replicate when applied to humans. We do not at this stage have any robust evidence of efficacy of PEA whatsoever.

Glucosamine

Anecdotally one hears a great deal about glucosamine and supplement manufacturers make strong claims for its effectiveness in reducing pain from osteoarthritis. A large meta-analysis by Liu et al[22] examined a wide range of commonly-recommended supplements including glucosamine and found none effective for pain. Less than 2% of patients experienced up to 20% improvement in pain (no different to placebo) and adverse reactions were common in all groups.

Physical/Mechanical Interventions

There is strong evidence for physical therapy as a strategy for achieving maximum strength and function directly following surgery or injury. However there is no such evidence for physical therapy for chronic pain and instead we find that physiotherapy is not superior (and may be inferior) to simply remaining active, as can be seen in the discussion below.

Rather than a physical therapy program, we can see that simply remaining physically and socially active, reducing stress, and improving nutrition particularly where overweight is an issue[50], maximises health generally. This benefit from physical activity is a basic truth that is applicable to everyone, including chronic pain patients – this is how we optimise our health status whatever that may be.

While a very small proportion of chronic pain patients may benefit from any of the physical/mechanical strategies discussed in this section, whether because it may actually have an effect for them, or whether it may merely be placebo (false attribution, regression to the mean, simple delusion/error of judgement) we have not been able to locate any definitive research regarding NNT [minimum number needed to treat in order to achieve at least 50% reduction in symptoms] or NNH [minimum number needed to treat for harmful side effects to appear], and for some we have strong evidence that there is no efficacy at all, but considerable potential for serious harm.

It is difficult to accurately assess the current cost of physical therapies of all kinds, but we can see from the Deloitte report of 2019[7] that hospital treatment, physiotherapy, and acupuncture together add up to approximately $5.2 billion per annum in Australia, without including the cost of aids or devices.

TENS

TENS, along with laser treatment, acupuncture, and pulsed magnetic devices, is no longer widely recommended for treatment of any pain, acute or chronic[6,51].

One Cochrane review[51] found that TENS did not improve pain or level of disability, and that there was no difference between conventional or "acupuncture-like" TENS.

The TENS (transcutaneous electronic nerve stimulation) machine was invented by Wall and Sweet after they hypothesized that stimulation of certain nerve cells seemed to diminish pain perception. It was initially believed that this was really the first breakthrough in the control of chronic pain, because it could be managed by the patient himself, it seemed to allow reduction or even elimination of drugs, and seemed to have no unwanted side effects.

However studies showed that not everyone benefited (to be expected because in true chronic pain it is no longer the injury site that is generating the pain in any case) and even people who did initially seem to respond, became less and less responsive to it over time, so it ended up not providing any relief at all. This is typical of placebo.

TENS did not treat the cause of the pain, and did not prevent the re-occurrence of pain, but tried to "dampen down" pain perception, perhaps "taking the edge off". TENS has been shown in 15 out of 17 randomised controlled trials to have no benefit compared to placebo[6].

Currently there is an advance on the TENS machine which is surgically implanted at a cost of around $AU40,000. There is no evidence that this more invasive alternative is any better[52].

So TENS and its successor are no panacea, but they might work, in a very limited way, for a short time, for some people, initially as a distraction, but overall probably in the same range as placebo.

It's an expensive way to fail to get relief.

Pulsed Electro-Magnetic Devices

There are many of these on the market, ranging from cheap to very expensive. Regardless of price, quality studies have consistently shown that they do nothing for chronic pain (or acute pain) despite the manufacturers' and salespeople's claims to the contrary, and despite their referencing studies that in no way support their claims.

A major Cochrane Review[53] concluded: "The overall pooled effect size was small and not statistically significant ….. Though the available evidence suggests that electromagnetic field stimulation may offer some benefit in the treatment of delayed union and non-union of long bone fractures, it is inconclusive and insufficient to inform current practice. More definitive conclusions on treatment effect await further well-conducted randomised controlled trials".

A positive study by Hong-fei et al[54] also concluded that PEMF devices could help to accelerate healing of long bone fractures, but the data shows a failure rate in excess of 30%, and only slightly faster healing than the sham treatment group, both taking months in any case.

This is yet another example of a paper claiming statistical significance which is not in any way clinically meaningful, along with a conclusion which is not supported by the data provided.

Hydrotherapy

Hydrotherapy can be thought of as water-based physiotherapy. Studies into the efficacy of hydrotherapy have been confined to cases of lower back pain (the most common of all chronic pain) and showed short-term effect in the range of an average 50% reduction in reported pain (good but not great in any case).

However, any benefit is very temporary and typically there is a complete return of pre-program pain levels just 3 months later[55].

So while it appears hydrotherapy can potentially provide partial relief from chronic pain in the lower back, it doesn't solve the problem, and is something that one must keep doing. If the sufferer enjoys hydrotherapy and does experience significant reduction of pain, then perhaps this is immaterial. Perhaps it is possible that if the sufferer achieves a result, and they keep doing it for long enough, their brain will "forget" how to trigger inappropriate chronic pain signals.

After all this is a well-known characteristic of conditioned responses. In the absence of a "reward" formerly associated with a particular stimulus, (inhibition process or "extinction learning") the response will sometimes fade off. This "wearing off" is well accepted as part of classical conditioning theory[56].

We haven't found any study which compares hydrotherapy with (for example) simply taking a brief daily stroll. So it's important to note that there is not currently evidence that hydrotherapy is superior to any other physical activity the chronic pain patient may engage in.

Physiotherapy

According to the World Health Organisation (**https://www.who.int/dietphysicalactivity/pa/en)** inactivity is one of the leading direct causes of death and disease in the Western world *"physical inactivity (lack of physical activity) has been identified as the fourth leading risk factor for global mortality (6% of deaths globally). Moreover, physical inactivity is estimated to be the* ***main cause*** *for approximately 21–25% of breast and colon cancers, 27% of diabetes and approximately 30% of ischaemic heart disease burden."*

Stated bluntly, lack of activity makes people physically and mentally sick, and even kills them.

So without doubt everyone needs to be active, meaning that we have around 1 hour of aerobic activity at least 4 times each week, and around 20 minutes of resistance (weight bearing) activity at least 3 times each week.

One of the challenges to being active is that people with pain have an instinctive desire to withdraw from activity and tend to be very fearful of even normal aches, pains, or soreness from being active. A chest pain that an athlete takes no notice of because to him/her it is insignificant, might be a traumatic event to someone with chronic pain who is in deep fear of damaging himself, or is fearful that the pain actually means something.

Another problem is that where chronic fatigue is part of the array of symptomatology, vigorous exercise can be deleterious to the person's mental and physical health. This is even more the case where a disorder such as Sick Euthyroid Syndrome has been diagnosed[57].

A recent review of Cochrane Reviews[58] found modest or nil improvement in pain levels of chronic pain patients participating in exercise programs.

Another study by Nilay et al[59] is representative of many papers purporting to demonstrate benefit of physical therapy for chronic pain. However closer examination of the data shows that although there was an average >25% reduction in pain, the average VAS went from 6.1 to 4.7 whereas the control group went from 5.2 to 5.0. In the treatment group this >25% reduction is a reduction of not even 2 points on the scale, which could be attributable to placebo effect (false attribution, regression to the mean, simple delusion/error of judgement) or could be attributed to therapist effect or experimenter effect.

Appropriate and carefully graded exercise programs are associated with reduced levels of pain, but there is little evidence that it is the specific physical therapy that is helping to gain that reduction for anyone other than those in a rehab phase of recovery (ie, not chronic pain patients).

Studies by Lopez et al[60] and Frost et al[61] demonstrated that for chronic pain, physiotherapy has no clinical benefit beyond any other increase in activity levels. This study found that any kind of activity is helpful to low back pain patients, and people who take up an "active hobby" (sport, social groups, artwork such as painting or sculpting, for example) do better than people who undertake physical therapy.

No-one would disagree that physical therapy can be critical in the case of acute injury or after surgery and is essential in order to regain strength and mobility. However this is clearly not the case for chronic pain patients. When the latter respond to physiotherapy, it is more likely that

1 The social aspects of exercise help to lessen the patient's anxiety and thereby serve to quieten the nervous system.

2 The time, care and nurture provided by the physical therapist makes the person feel comforted, safer and more relaxed.

3 The well-known health benefits (mental and physical) of exercise, if they are otherwise inactive, create greater wellbeing and reduce the impact of pain perception.

4 Chronic pain patients who become more active, tend to have less pain than those who are relatively inactive[61].

According to the latest Deloitte report[7], the cost of physiotherapy specifically for chronic pain is $165.8 million per annum in Australia, for little or no benefit. We do not have evidence at this time that this spend can be justified, unless it is directed at helping people to be more active generally.

Surgical interventions

Referring to Medicare statistics as reported by Deloitte[7], the cost of surgical intervention for chronic pain was estimated to be $64.4 million in the previous 12 months. This includes knee and hip repair or replacement, as well as spinal surgery.

As a last-resort effort to eliminate chronic pain, surgeons sometimes proceed to actually cutting a nerve branch. Initially this can (not always) achieve a seemingly miraculous result, although often at the cost of reduced mobility or loss of sensation[52,62].

Studies show that the nerve regenerates, although sometimes unfortunately in an unhelpful (undifferentiated) way, and because of that, pain can be even greater after surgery than it was before[62].

Compounding this is the fact that clinical trials designed to test usefulness of surgical procedures for chronic pain show that sham surgery to backs and knees achieves the same outcomes as actual surgery[63]. Whether in the surgical group or the sham group, the same proportion of patients experience improvement, experience deterioration, or experience no difference to their pain.

This lack of demonstrated efficacy for surgical intervention may be better understood when we realise that, for example, MRI and X-Ray images are not different between people who have chronic pain and people who are pain free, even when we include in the comparison athletes competing at an elite level[64].

This non-correlation of damage or "wear and tear" of the spine is why MRI and X-Ray are no longer recommended in the diagnosis of chronic pain[65].

We don't at this time have evidence that spending $64.4 million per annum on surgical interventions is warranted or effective. We must surely seek out a better treatment for chronic pain so that this last resort, risky intervention can be avoided in more cases.

Acupuncture

We spend some $24.9 million per annum on acupuncture specifically for chronic pain[7].

While there is no doubt that acupuncture enjoys widespread support amongst professionals and the general public alike, and even appears as an appropriate treatment on government health sites and can be eligible for Medicare funding, there is no evidence for any health benefit whatsoever, for anything. No valid studies suggest that acupuncture provides relief or a cure for chronic pain. On the contrary, countless studies show that acupuncture is no better than placebo, and fake acupuncture (where there is not even a needle) gets the same results[66].

At this moment we have over 3000 trials of acupuncture, and not one validated trial shows any benefit. Many are regarded as suspect as they have come out of China, where academics are known to commit fraud in order to get published in a Western journal[67]. According to Retraction Watch, China has a greater number of retractions of papers on acupuncture than the rest of the world combined (https://www.nytimes.com/2017/10/13/world/asia/china-science-fraud-scandals.html).

One such study by Dehua et al[68], which on the surface appears to be a randomised controlled trial demonstrating remarkable results for acupuncture, in fact had no experimenter blinding, was confounded by other simultaneous treatments (ended up testing electrical therapy, not acupuncture and was therefore what is called a "bait and switch" trial), confounded by subjective assessments of outcomes, made no attempt to measure whether or to what degree participants complied with their medication programs over the duration of the trial and follow up, failed to propose any biological mechanism, and had a deep conflict of interest in relation to the experimenters' need to validate acupuncture. It is troubling that this paper succeeded in being published in the prestigious journal JAMA.

A recent article in Lancet, in a continuing series of exposés on Chinese research (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32933-2/fulltext), revealed that there has never been a negative paper regarding acupuncture come out of China, and outlined steps the Chinese government is taking to try to eliminate rampant fraud that is still currently being committed in papers across many fields.

Some Australian studies are no better, with Cohen et al[69] reporting the unlikely outcome of acupuncture in the emergency department providing equivalent pain relief to strong analgesics, but even the authors admit there is no mechanism of action. Close examination of this trial reveals lack of sham control, complete lack of blinding, acupuncture compared to treatment with an inappropriate comparator (which was also known to be ineffective), treatment group consisting of back or ankle pain, both of which are known to be hugely variable in pain presentation, and other serious flaws. Regardless, acupuncture-only patients required higher levels of opioids as "rescue" treatment, and there was not a clinical or statistical difference between groups. All groups had very poor pain control, which is a known issue. Despite the claims of the authors, acupuncture did not provide a benefit, and led to higher opioid use.

Unfortunately, not only are we wasting many millions of dollars every year on acupuncture, but we are also wasting time, energy, money, and resources on researching an intervention which has been time and again clearly demonstrated to have no valid mechanism, and no beneficial effect, for anything.

Chiropractic and Osteopathy

As difficult as it is to design randomised, double-blind, controlled studies of these treatments, there is no validated evidence that they make any significant difference to chronic pain levels whatsoever.

An important Cochrane update[70] downgraded an earlier review where these interventions were declared "clinically insignificant" to an even worse conclusion of "non-existent effects" and stated that "SMT [spinal manipulation therapy] is no more effective for acute low back pain than inert interventions, sham SMT or as a adjunction therapy". It concluded that the only clear assumption which can be made from these studies is that the more "fanfare" which accompanies treatment (this includes all of the actions which accompany the procedure, as well as the way the clinician dresses), and the more hospital-based the treatment, and the longer the treatment sessions (even where the treatment was a placebo) the better the improvement of the patient.

In other words, it was not the treatment itself which determined whether the patient gained improvement. Regardless of whether "real" treatment was utilised or placebo treatment, what

did determine improvement were things like whether the intervention took place in a hospital setting, or how long the treatment lasted, or whether the clinician wore a white coat.

Given that there is no valid research supporting these modalities, and that real harm can be done (and frequently is done)[71,72], and that they distract the patient from other bona fide treatment which could help, it is difficult to understand how they could be recommended. They certainly should not be paid for out of the public purse.

Psychological Interventions

We were unable to locate a single paper, systematic review, or meta-analysis which demonstrated a clinically significant effect on chronic pain levels for psychological interventions currently in use, being variations of CBT (cognitive behaviour therapy), mindfulness, EMDR (eye movement desensitisation and reprocessing), and many others.

A systematic review and meta-analysis by Pike et al[73] was representative of studies and papers addressing the utility of psychological interventions for chronic pain, and concluded by claiming that psychological interventions were useful for reducing catastrophic thinking, but had no impact on health, on return to work, or on medication levels.

There is considerable evidence that no psychological strategy has any effect at all on chronic pain, as well as evidence that any improvement in quality of life scores is due to the therapeutic liaison, independent of any intervention.

It isn't possible at this time to determine how much is spent on psychotherapy for chronic pain clients in Australia, and the latest Deloitte report fails to include this sector, possibly for good reason.

Cognitive Behaviour Therapy (CBT)

Cognitive Behaviour Therapy has been used since the 1960s to treat a wide range of problems, such as anxiety and depression for example. In recent years it has also been used to treat chronic pain.

CBT is based on the belief that our thoughts and behaviours feed back into our nervous system and help to maintain problem states, claiming that it is our thoughts and behaviour which cause our suffering. In CBT, the psychologist seeks to identify the sorts of unhelpful thoughts and behaviours that the client has, and to stop them, by the use of logic and willpower and the dedicated practice of more rational or more positive self-talk.

It's not surprising that there is a high drop-out rate[74,75], not only among patients but also among therapists, because CBT can be perceived as deep criticism of the patient (basically blaming the patient's suffering on his/her thinking) and in any case the results are far from exciting[76]. After all, its aim is not to switch the pain off, but to help people to "accept and live with" their pain, or to "manage" their pain, or to stop "catastrophising" their pain.

CBT may not be all wrong in its *theoretical* basis. Studies do show that where people engage in avoidant thoughts or behaviours, their reported pain levels tend to be higher[77]. However we should keep in mind that correlation is not causation, and higher pain levels could readily create more avoidant thoughts and higher distress levels.

Although there are by now many studies which report glowing results for CBT, there are so many flaws in the study designs, and the effect sizes being reported are so low in any case, that we really cannot accept these glowing conclusions at face value. We need to recognise that modern meta-analyses of CBT studies provide strong evidence that effects, if any, are extremely short term, and that CBT produces results no better than placebo[78,79].

Many studies conclude with statements about CBT being the "gold standard" but a careful analysis shows this statement is not supported by the very data it is based on. In addition many studies have attempted to prove superiority of CBT by comparing with inappropriate or uninformative controls, such as waiting lists, or other equally ineffective treatments such as mindfulness, or analgesics which are known to have a high failure rate. CBT only looks superior (but nevertheless still not significantly efficacious) when compared to things that also don't work or don't work very well.

The Hofmann review of meta-analyses[78] is a case in point. Hofmann first makes a claim that CBT has strong evidence, but provides data and conclusions which demonstrate that CBT has a weak effect compared with waiting lists or no treatment, and is not effective in many cases.

The Faucett systematic review[79] examined several different types of treatment and found that in blind studies all interventions, including CBT, were better than doing nothing, but none were more effective than placebo.

While some people report that CBT has been helpful for them, we propose that it is not the CBT which was helpful, but the support of an empathetic professional with whom they had an excellent therapeutic liaison. It is generally accepted that the quality of the therapeutic liaison from the client's perspective (not from the therapist's perspective), is the single most important determinant of a clinically-significant outcome[80] and that the utilisation of CBT is not a significant variable in predicting outcomes. Cuipers et al[81] however proposed that this is not necessarily the case, bizarrely giving as a rationale a claim that it's not been possible to show that any one therapeutic strategy is superior to any other, and that to date all studies have been correlational.

Quite clearly, when we examine any of the currently utilised therapies, efficacy and effect size are similarly modest, small, or nil.

A recent paper by David et al[82] was entitled "Why Cognitive Behaviour Therapy is the Current Gold Standard of Psychotherapy". This paper is a both a meta-analysis of CBT itself, and a rationale for the reputation of CBT as "gold standard" of treatment.

However David's paper, similar to all studies of CBT which I have explored in an effort to find a single one with a significant effect size:

- Contains glaring errors in critical thinking
- Overplays the significance of the data, even while stating that outcomes "are not very good"
- Attempts to justify CBT as "gold standard" even though the data to support that is lacking
- Claims that CBT is a "paradigm" which encompasses all therapy, despite not even proposing a verifiable mechanism, let alone any complete theoretical basis

In David's paper the authors begin by claiming that CBT is "arguably" the "gold standard" because of the sheer "number of publications/studies, academic programs, and/or practising professionals". Popularity cannot be regarded in any way as evidence for efficacy, and all that this popularity may indicate is that a seriously ineffective treatment strategy has been able to penetrate and permeate the market.

This would be far from the first time, because even in the recent past we have seen similar uptake of acupuncture, homeopathy, naturopathy, "learning style" theory, "left/right brain" theory, ego depletion theory, priming theory, positive psychology, growth mindset, and many, many others that even though they have been thoroughly debunked, continue to be promoted and in some cases are actually growing in popularity even amongst health professionals who should know better. Mass acceptance does not equate to substance, and as we've seen, health professionals can be just as gullible as the general public.

The edited text "Science and Pseudoscience in Clinical Psychology"[83] contains a litany of pseudoscientific hypotheses and practices that have polluted the field of psychology in terms of both research and clinical practice since the beginning of the field, and which continue to do so to this day. Indeed we have professors in universities around the world, including Australia, who have built their careers on pseudoscience and who continue to promote it to this day, as well as universities themselves accepting sponsorship money in return for undertaking research on interventions already demonstrated to be completely useless.

Most health professionals are not scientists, and are not trained in critical thinking, and so it is the case that when they see temporary client improvement in their office, they make the unwarranted assumption that their treatment has been effective. Likewise they are generally not trained in analysis of research and tend to be uncritical of poor research which nevertheless offers conclusions which supports their optimistic assumptions[84].

Even David et al[82] states unequivocally that studies supporting CBT have been of such low quality that the status of CBT can be seriously challenged. In paragraphs 2 and 3 the authors state that CBT is not the best standard *possible*, but the best we have currently. In other words, David acknowledges that CBT is not very good, but without offering any evidence, at the same time claims CBT is better than anything else which is also not very good.

This latter statement by David is founded on his claim that no other form of psychotherapy has been shown to be "systematically superior" to CBT. However well-designed studies show that CBT is not "systematically superior" to placebo.

Well-designed studies investigating chronic pain treatment show that *none* of the current treatments, being a great number of medications, physical therapy, and psychological interventions such as CBT or mindfulness, are significantly superior to placebo[20] for the majority of people.

So the fact that none of these things are superior to CBT is in no way supportive of CBT as a therapy, because CBT is not superior to these other interventions either. Like most treatments for chronic pain, CBT is also not effective for the great majority of people suffering from chronic pain.

Another analysis by Morley et al[85] attempted to show the effectiveness of CBT in enhancing positive affect and thereby achieving higher pain resilience. In marked contrast to that claim, this paper's conclusion included the statement "Half of the comparisons showed no effect of CBT and half showed weak effect sizes of unknown clinical significance on pain, mood, disability and catastrophic thinking outcomes".

Morley also used as evidence for CBT the fact that "the CBT theoretical models/mechanisms of change have been the most researched and are in line with the current mainstream paradigms of human mind and behaviour". I note that Morley's statement exposes a politically popular perspective here, not science, and the use of the word "mechanism" is outside its scientific meaning.

To understand why CBT fails it is helpful to examine its two-fold hypothesis. Firstly CBT can be defined as an inhibition strategy because in lab experiments with animals we see that extinction (of conditioning) can be achieved by deliberately separating stimulus and response (in a Pavlovian example this would be the equivalent of ringing the bell repeatedly without providing food). Secondly we have an hypothesis from neuroscience which says that conscious thought can suppress automatic impulses and alter behaviour. I will address each of these separately below.

CBT as an inhibition strategy: There can be no doubt that under laboratory conditions with animal subjects, inhibition can *eventually* result in extinction of a formerly conditioned response. Just as with animal studies generally, these studies do not translate to the human experience. Human beings are far more complex psychologically, and do not exist in laboratory conditions. We live in complex environments, which we traverse by means of complex networks of conditioned responses which are being constantly reinforced by that environment, including in ways we are not even consciously aware of. We do not have any significant evidence that inhibition is an effective strategy in humans, and reappearance (or relearning) of the unwanted thought, feeling, or behaviour is notorious, particularly under stress or threat conditions.

Neuro feedback: When we use self-talk to try to achieve self-control to resist unhelpful impulses, we are engaging in suppression, not in elimination of the impulses altogether. Although there are studies purporting to show benefit from mechanical neuro feedback, the science is highly controversial, to the degree that Psychology Today actually warned people against spending money on it. Suppression does not extinguish the impulse, and as with other inhibition strategies, notoriously fails under conditions of stress or threat.

The David[82] paper discussed previously concludes by making an unsupported claim that no other psychotherapy has changed or evolved but that CBT is an "evolving psychotherapy" and that future improvements in psychotherapy generally will derive from CBT.

Since the theory and principles of CBT are so flawed (including having no verified mechanism), and the claimed outcomes absent, small or inconsequential compared to placebo, this is not a foundation for improvement of the practice of therapy. We need to see CBT for what it is, no better or more relevant than homeopathy, and leave it behind as an embarrassing anachronism in a field which is littered with unproven hypotheses and philosophies, rather than having scientifically validated theories and practices as a foundation.

Mindfulness

Mindfulness can be regarded as another name for Acceptance and Commitment Therapy (ACT). It comes directly from Buddhist meditation practice, first gained a foothold in Europe, and now unfortunately has spread worldwide and is popular amongst psychologists, even though so far valid studies show it to be of no or little effect[86,87], and clearly not superior to anything else someone may do for recreation.

A significant quantity of poor-quality, flawed studies claim to show benefit. Peer reviews of those studies basically debunk them and make it clear that mindfulness is no more beneficial than other forms of relaxation, such as reading a book, listening to music, taking a nap, or going for a walk[88].

Buddhists refute the unwarranted claims for mindfulness, neuroscientists are horrified by the hype, and are also deeply concerned that mindfulness has been corporatized in a way that is intended to support employees to tolerate unnecessarily stressful conditions instead of fixing the conditions[89].

In mindfulness one mindfully contemplates and recognises one's thoughts and experiences and "accepts" them, which supposedly reduces suffering. Proponents of mindfulness make all kinds of claims for health and wellbeing and this is what deeply annoys neuroscientists, who say this is a hyped-up claim and that mindfulness studies are of appalling quality[88].

We find it deeply concerning that people are asked to spend hours "belly-button gazing" their pain and distress, especially when issues need to be resolved, or when it's possible to simply eliminate those things very rapidly and permanently, without fuss. In other words, mindfulness should not be used to manipulate people into putting up with things they have no need to put up with[90].

In addition, mindfulness is a sedentary "activity" that therefore does not contribute to mental or physical health in the way that an active recreational choice is proven to do.

Studies purporting to show benefit from mindfulness have indeed been so atrociously designed that they are fatally flawed and few or no conclusions can be drawn from them. In addition, it is recognised that mindfulness can actually be dangerous for some people with particular psychological disorders, or who are facing real stress in their lives, and can lead to anxiety, panic attacks and depression[90]. It is terrifying that it is being used in schools by practitioners who are not trained to recognise contra-indications and likewise may not even recognise that damage is being done. At a time when critical thinking skills are in dire need, we should not be enabling anti-critical, anti-science principles and practices in our school populations.

In addition, when we expose the general public to psychology-endorsed quackery we don't just promote gullibility, we also teach people to denigrate science and increase disrespect and resistance to health experts who are doing their best to promote good health practices that are scientifically based.

There is no indication at all that many hours of mindfulness (which is what it is claimed is necessary before "results" can be experienced) are superior to a brief walk, a nap, having a hobby, kicking a ball around, watching television, listening to music, or spending time relaxing with friends or family. We should not be pushing clients to spend so much time and effort

learning and using a spurious technique when they can get better and faster benefits from doing far more rewarding and beneficial activities.

In a paper published in the journal "Perspectives on Psychological Science" in October 2017[91], the author claimed that current research on mindfulness was completely unsatisfactory, and said: "As mindfulness has increasingly pervaded every aspect of contemporary society, so have misunderstandings about what it is, whom it helps, and how it affects the mind and brain. At a practical level, the misinformation and propagation of poor research methodology can potentially lead to people being harmed, cheated, disappointed, and disaffected".

A comprehensive meta-analysis and review was carried out for the US Agency for Healthcare Research and Quality[92]. This paper screened over 19,000 citations and could find only 47 that were of sufficient quality to analyse. Nevertheless it included the scathing commentary: "The modest benefit found in the study …. begs the question of why, in the absence of strong scientifically vetted evidence, meditation in particular and complementary measures in general have become so popular, especially among the influential and well educated…What role is being played by commercial interests? Are they taking advantage of the public's anxieties to promote use of complementary measures that lack a base of scientific evidence? Do we need to require scientific evidence of efficacy and safety for these measures?"

Allan Goroll, a doctor at Harvard University said of this analysis: "Contrary to popular belief, the studies overall failed to show much benefit from meditation with regard to relief of suffering or improvement in overall health."

A more recent study by Collins et al[93] found that daily playing a game of Tetris on a mobile phone both in the laboratory and in the field in relation to work stress was superior to mindfulness in terms of increasing energy and job satisfaction, and reducing stress. Mindfulness was associated with decreasing energy levels.

At this stage we do not have any evidence that investing public money in mindfulness training or treatment is of any benefit. Some people may enjoy it, in the same way that they may enjoy a massage, or enjoy a hobby, and that is a matter of personal choice, not a matter for the public purse.

EMDR (Eye Movement Desensitisation and Reprocessing)

In EMDR the therapist has the client mentally focus on a "trigger thought" while experiencing some bilateral stimulation which may be a side-to-side finger or wand movement which the client tracks visually, or a buzzer on each hand (for example).

It is often said about EMDR that "what works is not new, and what's new does not work". Indeed a meta-analysis of 4 studies by Davidson et al[94], and another meta-analysis of 7 studies by Verstrael et al[95], found that EMDR achieved outcomes no different to exposure (to the trigger thought or memory) alone, ie; without the use of bilateral stimulation of any kind.

EMDR was developed as a treatment strategy by the late Francine Shapiro[96] in the late 1980s. Two different mechanisms of action have been put forward, both of which have been invalidated.

Shapiro's first hypothesis arose after she experienced personal relief for a troubling issue after walking through a forest while ruminating the issue. As she later wondered about the cause of the sudden relief, she recalled that she had been looking from side to side as she walked. She believed that these saccadic eye movements were similar to those in REM (rapid eye movement) sleep and that this signified an unconscious processing of trauma, just as it is thought that we use sleep to process and recover from trauma or simple stress.

However fMRI shows that eye movements are not accompanied by the same brain activity as REM sleep. Pagani et al[97] tried to show that saccadic eye movements and REM produced the same brain activity but failed, and finally had to agree with an earlier study by Stickgold et al[98] "We are not claiming that we have solid evidence for all of the links and interpretations in the train of logic presented here", weasel words to get around the fact that the fMRI data did not support the hypothesis.

When this hypothesis was debunked, Shapiro switched her hypothesis to propose that EMDR was causing a "rebalancing" of the left and right hemispheres of the brain and that this in turn caused processing of the traumatic material and a return to more adaptive feelings, thoughts, and behaviours. Similar to the REM hypothesis, fMRI has not supported this one either.

So as seen in various meta-analyses, the eye movements or other bilateral stimulation do not approximate REM sleep, do not "rebalance the hemispheres" and are not an improvement on exposure therapy alone. Santarnecchi et al[99] found no difference in fMRI pre- and post-treatment between clients using CBT or clients using EMDR.

It is more likely that any benefit of EMDR is therapist related (the therapeutic liaison[81]), or may be from an exposure effect. Since the most "successful" EMDR studies were run by Shapiro herself, including administering the testing instruments, it is also possible that "experimenter expectation" may have played a role in her apparent success[100].

It is also possible that EMDR may sometimes inadvertently trigger a disruption of reconsolidation of a conditioned response[101] (as in SDR Therapy). That is certainly not the theory or the aim of EMDR treatment, but disruption (and extinction) may occur accidently during treatment if the client is helped to identify and accurately maintain the triggering of a precise enough stimulus to an unwanted response, and if a simultaneous disruptive factor is intense enough and provided precisely enough to serve its purpose of disruption of reconsolidation of the conditioned response. We will discuss this aspect in detail in a future paper, including describing an array of research on disruption of the reconsolidation phase of a conditioned response as an extinction strategy.

"Pain Education"

Mosely[102] has proposed that when people understand their chronic pain, they tend to report lower pain levels. While this might make sense intuitively, given what we know about the stress which may be experienced from not knowing or understanding[77] a recent trial putting this hypothesis to the test did not support the hypothesis and Moseley openly and humbly finally admitted that pain education is not the answer (article by Lorimer Moseley responding to trial by Traeger et al[103]: https://bodyinmind.org/explaining-pain-traeger-part-1/). Puzzlingly, Moseley has continued to promote his "Explain Pain" as an appropriate treatment for chronic pain and has built an educational organisation which teaches pain education around the world.

The trial by Traeger et al[103] above was the first real test of the hypothesis of utility of pain education, being the first trial to compare pain education with a placebo and concluded "Two 1-hour sessions of pain science education were no more effective than a placebo intervention for improving pain at 3 months, 6 months, or 12 months after the onset of acute low back pain."

Crucially, it was also noted that "Changing self-reported pain attitudes and catastrophising does not lead to less pain later". This finding also has enormous implications for the major focus of CBT on preventing people from catastrophising their pain because it shows up CBT for what it is, a whimsical concept that is not borne out by science.

And it is clear that "explain pain" or "pain education" is not a successful treatment for chronic pain, and therefore should only comprise a minor (if at all) part of a chronic pain treatment program because knowing that you shouldn't be experiencing the pain turns out not to have an effect on the pain.

None of this is surprising given that yet another 2015 meta-analysis by Traeger et al[104] tried to show that for low back pain, patient education could assist with "reassurance" of the patient and lead to fewer doctor visits. Although this paper concluded with a statement of value of patient education, that value was not demonstrated, and Traeger admitted that the NNT (number needed to treat) was 17 in order to avoid a single doctor visit. This really is clutching at straws in relation to trying to prove some monetary value of pain education.

Based on the available research on pain education, it is Sutherland's view that pain education is important from an humanitarian perspective, but that pain education is not pain treatment and does not significantly affect pain levels, nor psychological wellbeing. It is simply the decent thing to do in order to fully inform the patient, and it is important for health professionals to better understand chronic pain in order to better understand their client/patient.

Multi-disciplinary Care

Given the universally-recognised need to reduce costs and achieve better outcomes for chronic pain patients, there has been strong interest in promoting multi-disciplinary care[5], which is also referred to as "comprehensive care". However it is clear that the results are barely better than merely giving the chronic pain population paracetamol, achieving an average of only 30% reduction in pain levels[105], reducing at 12 months to only 21%[106].

The two latter studies mentioned here nevertheless include conclusions glowingly in favour of multi-disciplinary care, despite the poor efficacy, and despite nil effect on emotional distress due to pain[106].

The Deloitte report[7] on multi-disciplinary care concludes "Doubling Australians' access to multidisciplinary care to treat chronic pain could be achieved with a $70 million per year investment. Greater access to multidisciplinary care could deliver $3.7 million in savings to the health system (net of intervention costs) while also reducing other costs", but this is far from a certainty, and the report itself says "However, more robust evidence is urgently needed …".

A recent Canadian study[107] on comprehensive or multi-disciplinary treatment programs for non-malignant chronic pain without explanatory pathology also recommended such programs, but concluded: "the evidence on cost-effectiveness was limited".

It is not a good use of resources to include in a multi-disciplinary program interventions that are demonstrated to have nil or poor effect. It is deeply worrying to see a push toward bringing together the whole array of ineffective treatments in a vain hope of finally doing something about chronic pain. When something is not working, it does not make sense to do even more of it than ever before.

Clearly we need to be weeding out known ineffective interventions, particularly where they are one way or the other paid out of the public purse, and replacing them with far more effective treatments for non-malignant chronic pain without sufficient explanatory pathology, not only to reduce costs in a health system that according to Dr Stephen Duckett of the Grattan Institute, is in a "death spiral" but to finally put an end to needless suffering, and the accompanying burden not only on the pain patient, but on their families, workplaces, and communities.

SDR Therapy

Sensory Disruption of Reconsolidation (of conditioned responses), or SDR Therapy, is a novel treatment yet to be tested in robust clinical trials. Four pilot studies have shown promising results.

A full rationale for the use of SDR Therapy for chronic pain will be presented in a further paper, *"Frontiers in Chronic Pain: A Rationale for a New Understanding of Non-malignant Chronic Pain without Sufficient Explanatory Pathology and Subsequently a New Paradigm for Improved Treatment"* to be published shortly. This will be followed by a phase 3 clinical trial of SDR Therapy expected to take place in 2020.

SDR Therapy addresses an updated understanding that most non-malignant chronic pain without sufficient explanatory pathology is not nociceptive in nature, but that the pain signalling in these cases is mediated primarily via the amygdala region in accordance with classical conditioning theory.

As we've seen in the above notes, inhibition strategies are ineffective in dealing with conditioned responses. However new research indicates that disruption strategies executed during the reconsolidation phase of a conditioned response efficiently and permanently provide extinction.

We will address all of these issues in detail in following papers.

WHY DO CURRENT TREATMENTS FAIL?

The most obvious answer to this question is that treatments fail when they do not address the problem.

There is now considerable evidence that non-malignant chronic pain without sufficient explanatory pathology is a "brain problem" not a body problem, and that there are two aspects to this issue.

Firstly we see through the work of many scientists, such as Pike et al[73], Neugebauer[108], Lewis et al[109], De Koninck et al[110] and many others that chronic pain signalling is a conditioned response. None of the treatments currently being used extinguish, or even attempt to extinguish, these responses.

Secondly we understand that the nervous system can become over sensitive and this is backed by a considerable body of work demonstrating that persistent pain is associated with central sensitisation, where the nervous system is responding abnormally to "normal" changes in temperature, movement or pressure for example[111].

This second factor requires treatment which seeks to "rest" the nervous system and provide an optimum environment for the return of homeostasis, and this will involve attending to comorbidity such as depression and/or anxiety, as well as attending to critical issues such as sleep, nutrition, activity levels, stress, etc.

Some programs do attempt to address the second factor, not necessarily very well, but without extinguishing the conditioned pain signalling can have only limited impact if any.

WHY DO HEALTH PROFESSIONALS CONTINUE TO USE INEFFECTIVE TREATMENTS?

It's important to note that bona fide health professionals generally do their best to provide therapy that is "evidence based". At the same time examination of the papers cited by this paper will show that the great majority of these papers conclude with a statement of strength of evidence of the treatment being tested, despite the actual small or non-existent efficacy revealed. Indeed the statistical significance reported is often so small that it does not translate to clinical significance.

So it is logical that health professionals, unless trained to critically analyse research papers, will tend to accept the conclusions at face value, especially if the intervention or treatment is already in wide use as "treatment as usual". They do not generally realise that any real outcomes are most likely the result of the quality of the therapeutic liaison from the client's perspective[80], and not the particular modality they have employed.

As noted earlier in this paper, it is remarkably common that a therapist will over-estimate the impact of their work with the client, assuming that what they see in the clinic is representative of robust outcomes[84]. It is far from unusual to see acupuncturists extolling the virtues of acupuncture, and CBT or mindfulness proponents extolling the virtue of those, and yet these are mere anecdotes and are not borne out by the vast body of research literature to hand.

The result of all of this is that ineffective interventions have polluted the profession, and this is how we see therapists sticking with therapies that do not actually work.

In the case of the pharmaceuticals, there is at least some evidence that some medications or combinations of medications provide some small relief for a small minority of people, and even though this is a very low bar one could say in the absence of anything else it is at least worth trying from a humanitarian point of view.

CONCLUSIONS

At this time we do not have evidence of strong efficacy (or even moderate efficacy) for any treatment for non-malignant chronic pain without sufficient explanatory pathology, whether that be pharmacological, physical, or psychological, including the newer multi-disciplinary or "comprehensive" treatment programs.

Therefore we should move as quickly as possible to robustly test SDR Therapy as a novel approach in order to attempt to reduce suffering and also reduce costs of this extraordinarily expensive condition.

We should also immediately withdraw from use therapies which have no evidence whatsoever of utility, and also withdraw health rebates from these so that the public purse is not being stung by what constitutes subsidisation of snake oil.

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