DECEMBER 2022 VOLUME 20 ISSUE 4

PAIN NEWS

A PUBLICATION OF THE BRITISH PAIN SOCIETY

The effect of snow sunset Eragny. Emile Pissaro. 1895

ISSN 2050–4497

THE BRITISH PAIN SOCIETY
EXPERTISE WHERE IT MATTERS

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ELDERLY No dosage adjustment.

RENAL IMPAIRMENT No special dose adjustment.

HEPATIC IMPAIRMENT. Mild to moderate hepatic impairment: no need for dose adjustment, carefully monitor. Patients with severe hepatic impairment may accumulate buprenorphine. Consider alternate therapy in such patients.

CONTRA-INDICATIONS Buprenorphine or excipient hypersensitivity, opioid-dependent patients, narcotic withdrawal treatment, respiratory depression, use of monoamine oxidase inhibitors (MAOIs) within the past two-weeks, myasthenia gravis, delirium tremens.

PRECAUTIONS AND WARNINGS Use with particular caution in those with respiratory depression, CNS depressants co-administration, serotonergic agents, psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse, sleep apnoea, acute alcohol intoxication, head injury, intracranial lesions or increased intracranial pressure, shock, reduced consciousness of uncertain origin, severely impaired hepatic function, constipation, patients known to have, or suspected of having, problems with drug or alcohol abuse or serious mental illness. Long term treatment effects and tolerance, opioid use disorder (OUS; abuse and dependence) and withdrawal syndrome may occur; please see SPC for detailed advice. Concomitant use with sedative drugs (e.g. benzodiazepines) can result in sedation, respiratory depression, coma and death so concomitant use should be reserved for patients where alternative treatment options are not possible. May affect ability to drive and use machinery. Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia; the risk of CSA is dose-dependent. To minimise the risk of occurrence of application site skin reactions, it is important to follow the posology instructions; patients and caregivers should be instructed accordingly to monitor the application sites for such reactions. Not recommended for analgesia in the immediate post-operative period or in other situations characterised by a narrow therapeutic index or a rapidly varying analgesic requirement. Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder. Euphorigenic effects may result in abuse of **Bunov**. Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes (e.g. increase in serum prolactin, decreases in plasma cortisol and testosterone); clinical symptoms may be manifest.

INTERACTIONS Bunov must not be used concomitantly with MAOIs or in patients who have received MAOIs within the previous two weeks. Concomitant administration of buprenorphine with serotonin agents, such as an MAOI, SSRI or an SNRI or tricyclic antidepressants may cause serotonin syndrome - a potentially life threatening condition (symptoms may include mental status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms), see SPC for more details. Use in caution with CNS depressants (e.g. benzodiazepines, opioid derivatives, antidepressants, sedatives, alcohol, anxiolytics, neuroleptics, clonidine). CYP3A4 inhibitors, enzyme inducers (e.g. phenobarbital etc.), products reducing hepatic blood flow (e.g. halothane).

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SIDE-EFFECTS Very common (≥1/10) and common (≥1/100, <1/10) headache, dizziness, somnolence, constipation, nausea, vomiting, pruritus, erythema, application site reaction, anorexia, confusion, depression, insomnia, nervousness, anxiety, tremor, dyspnoea, abdominal pain, diarrhoea, dyspepsia, dry mouth, rash, sweating, exanthema, muscular weakness, tiredness, asthenic conditions, peripheral oedema. Uncommon (≥1/1000 to <1/100) and Rare (≥1/10,000 to <1/1000) hypersensitivity, sleep disorder, affect lability, restlessness, agitation, euphoric mood, hallucinations, decreased libido, aggression, sedation, dysgeusia, dysarthria, hypoaesthesia, memory impairment, migraine, syncope, abnormal co-ordination, disturbance in attention, dry eye, blurred vision, tinnitus, vertigo, palpitations, tachycardia, hypotension, circulatory collapse, hypertension, flushing, cough, wheezing, hiccups, flatulence, dry skin, urticaria, myalgia, muscle spasms, urinary incontinence, urinary retention, urinary hesitation, fatigue, pyrexia, rigors, oedema, drug withdrawal syndrome, application site dermatitis, chest pain, alanine aminotransferase increased, weight decreased, accidental injury, fall, anaphylactic reaction, dehydration, psychotic disorder, balance disorder, speech disorder, visual disturbance, eyelid oedema, miosis, angina pectoris, vasodilatation, orthostatic hypotension, respiratory depression, respiratory failure, asthma aggravated, hyperventilation, rhinitis, dysphagia, ileus, face oedema, erectile dysfunction, sexual dysfunction, influenza like illness, Very rare (<1/10,000) drug dependence, mood swings, involuntary muscle contractions, ear pain, pustules, vesicles. Frequency unknown anaphylactoid reactions, depersonalisation, diverticulitis, biliary colic, dermatitis contact, application skin discolouration, neonatal drug withdrawal, drug tolerance, seizures, sleep apnoea syndrome, hyperalgesia. Please consult the SPC for details of other side-effects.

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MARKETING AUTHORISATION HOLDER Glenmark Pharmaceuticals Europe Limited, Laxmi House, 2B Draycott Avenue, Kenton, Middlesex HA3 0BU United Kingdom

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PP-UK-Bun-0007 V2 August 2022

References:

1. Data on file – Bunov (buprenorphine) is the fastest growing 7-day buprenorphine transdermal patch (Glenmark Pharmaceuticals Ltd). BUN/2022/04/002;
2. Data on file –Ratio of Bunov price to generic/tariff pricing (Glenmark Pharmaceuticals Ltd). BUN/2022/04/001;
3. Public Assessment Report. Bunov transdermal patches (Glenmark Pharmaceuticals Ltd); **4.** NHS Specialist Pharmacy Service. Example medicines to prescribe by brand name in primary care. Available at: https://www.sps.nhs.uk/articles/example-medicines-to-prescribe-by-brand-name-inprimary-care/; **5.** Bunov Summary of Product Characteristics (SmPC). Available at: https://www.medicines.org.uk/emc/search?q=bunov.

PP-UK-Bun-0030
September 2022

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PAIN NEWS is published quarterly. Circulation 1300. For information on advertising please contact
Neil Chesher, SAGE Publications,
1 Oliver's Yard, 55 City Road,
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Email: advertising@sagepub.co.uk

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ISSN 2050-4497 (Print)
ISSN 2050-4500 (Online)
Printed by Page Bros., Norwich, UK

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https://www.britishpainsociety.org/for-members/pain-news/

Editorial

Healing the healers Part 3: when we find ourselves in a dark wood

Pain News
2022, Vol 20(4) 86–88

Dr Rajesh Munglani

The Fall of Icarus Peter Paul Rubens. 1636. Royal Museums of Fine Arts of Belgium, Brussels, Belgium.

> Nel mezzo del cammin di nostra vita
> mi ritrovai per una selva oscura,
> ché la diritta via era smarrita.
>
> Ahi quanto a dir qual era è cosa dura
> esta selva selvaggia e aspra e forte
> che nel pensier rinova la paura!
>
> Midway upon the journey of our life
> I found myself within a forest dark,
> For the straightforward pathway had been lost.
>
> Ah me! how hard a thing it is to say
> What was this forest savage, rough, and stern,
> Which in the very thought renews the fear.
>
> Dante Alighieri, The Divine Comedy *Canto 1*:
>
> *The Dark Wood and the Hill*

If you are a doctor working in the United Kingdom, you should expect to be the subject of a General Medical Council (GMC) complaint at some point in your career. The GMC receives around 7,000–8,000 complaints every year.[i] Based on the number of doctors on the GMC register, there is an approximate 2% yearly chance of being subject to a complaint and so in a typical 35-year career, it is more likely than not an individual doctor will be the subject of at least one complaint to the GMC within a working lifetime.[ii]

While there is always something one wishes one could have done to avoid being subject to a complaint, perhaps we should accept and indeed expect such things to happen regardless of how careful we are in treating our patients and dealing with our colleagues.

Icarus was foolish to try to fly towards the sun in wings held together by wax – a sign of complacency or hubris, perhaps? It was foreseeable the wax would melt as he flew too close to the sun – in fact, he had been warned of exactly this danger by his father, the master craftsman Daedalus.[iii] This myth suggests that at least some troubles in life may be predictable and therefore avoidable. Often, however, problems in life are neither foreseeable nor preventable. Problems in life often occur without warning and one may, like Dante, find oneself unexpectedly lost in a dark wood.

Every year March 25 is celebrated as Dante day. Dante was born in Florence in 1265. He was a cavalryman, proud that his ancestors were descendants of the Roman soldiers who settled along the banks of the Arno.

Dante is said to have met Beatrice Portinari, when he was nine and she was eight, and to have fallen in love with her ‘at first sight’, apparently without even speaking to her. When he was 12, however, as was typical in those days, he was promised in marriage to Gemma di Manetto, a daughter of the powerful Donati family.

Dante studied and excelled at Tuscan poetry and is now considered to be the father of the modern Italian language because he wrote his famous works, including the *Divine Comedy* (*Commedia*), in the vernacular Italian rather than in

Latin. The Commedia is considered one of the greatest works of European literature.

Dante was always ambitious in the political life of his birth city of Florence. Tragically, his views eventually landed him on the losing side. His party, the White Guelphs, supported freedom from papal interference in Florentine affairs. The opposing Black Guelphs supported the pope in Rome. After much intrigue and changes of government, the Black Guelphs triumphed.

Falsely accused of corruption and financial wrongdoing, Dante was exiled from Florence for 2 years in 1302 after he refused to pay a fine. Thereafter, he was banned for life, threatened with execution at the stake or by beheading. Dante refused any pardon that required him to admit guilt against his beloved city. For the next 20 years, the poet travelled from place to place in Tuscany and elsewhere. His final years were spent in the city of Ravenna on the Adriatic coast, where ultimately he died of malaria in 1321. In the opening of the part-prose and part-poetical *Divine Comedy*, Dante describes finding himself unexpectedly in a dark wood. The *Divine Comedy* describes Dante's journey through Hell (*Inferno*), Purgatory (*Purgatorio*) and Paradise (*Paradiso*), guided first by the ancient Roman poet Virgil and then by his (unrequited) childhood love, Beatrice.

Many of us will find ourselves in such a dark place despite having done little to deserve it and, importantly, having no control of the circumstances why we ended up there.

The question to ask is not, 'Why me this time in this place?' but, 'What can I learn from this experience?'

As the philosopher Alain De Botton said, 'We should not feel embarrassed by our difficulties, only by our failure to grow anything beautiful from them'. De Botton also said, 'The difference between hope and despair is a different way of telling stories from the same facts'. We may not be able to change circumstances but we may allow the circumstances to transform us. During the course of our journey through the dark woods, we will likely learn some embarrassingly basic and stupidly obvious things about ourselves and we will have the opportunity to become better for it. Admitting to these vulnerabilities to others and even perhaps to be able to smile gently and laugh softly about our weaknesses and responses to such events, without bitterness, is at once both a deeply healing and attractive quality.

If we suffer the collapse of our life including our working world, what others think of us can be a great burden to bear. The loss of our status and reputation will cause us much soul searching to re-evaluate what is actually important.

We have, in modern times, ascribed much too much value to work. We have to remember, for most of history work was not expected to be meaningful, lucrative or fulfilling. In a time of crisis, we need to be able to find what has worth and meaning.

For, as the Stoic philosophers recognise, we may have little or no control over the onset of circumstances and failure, and because of this viewpoint the Stoics believed that a wise person would always be prepared for such drastic swings of fortune. In advance, in times of peace and tranquillity, they would practise 'negative visualization'. That is, they would imagine the worst – the events that could lead to what they feared the most – and mentally prepare themselves. So when disaster finally struck, they would not be surprised by it. Seneca wrote that 'nothing happens to the wise man contrary to his expectation'.

Yet usually, failures are devastating to us – failed businesses, failed relationships, failed vacations and failed attempts to get across town in 15 minutes are due to the fact *we failed to consider that things could happen any other way but the way we wanted them to.*

The wiser person is aware of all possibilities and prepared for all of them. In this way, there is no such thing as failure – simply different *outcomes. Our task is to make the most of that outcome.* Marcus Aurelius wrote, 'The impediment to action advances action. What stands in the way becomes the way'. Everything – good and bad – is an opportunity to practise virtue. One of the simplest examples is that when you are stuck in heavy traffic (on the M25 or here in Oxford), use it as a chance to learn patience and accept that most things in life are out of your control.

The Stoics recognised four virtues.[iv]

Wisdom

The chief task in life is simply this: to identify and separate matters so that I can say clearly to myself which are externals not under my control, and which have to do with the choices I actually control. Where then do I look for good and evil? Not to uncontrollable externals, but within myself to the choices that are my own. (Epictetus)

Temperance

'If you seek tranquillity, do less'. Or (more accurately) do what's essential – what the logos of a social being requires, and in the requisite way. Which brings a double satisfaction: to do less, better. Because most of what we say and do is not essential. If you can eliminate it, you'll have more time,

and more tranquillity. Ask yourself at every moment, 'Is this necessary?' (Marcus Aurelius, *Meditations*, 4.24)

Courage

Don't you know life is like a military campaign? One must serve on watch, another in reconnaissance, another on the front line. ... So it is for us–each person's life is a kind of battle, and a long and varied one, too. You must keep watch like a soldier and do everything commanded. ... You have been stationed in a key post, not some lowly place, and not for a short time but for life. (Epictetus, *Discourses*, 3.24.31–36)

Justice

And a commitment to justice in your own acts. Which means: thought and action resulting in the common good. What you were born to do. (Marcus Aurelius, *Meditations*, 9.31)

Justice was considered by Marcus Aurelius to be the highest virtue. Cicero, in speaking of Justice, described it as 'The principle which constitutes the bond of human society and of a virtual community of life'. Closely allied to the concept of Justice is *Sympatheia* – the belief in mutual interdependence among everything in the universe, that we are all one. Marcus' favourite philosopher, the Stoic teacher Epictetus, said, 'Seeking the very best in ourselves means actively caring for the welfare of other human beings'. And in turn Epictetus' teacher, Musonius Rufus, said, 'To honour equality, to want to do good, and for a person, being human, to not want to harm human beings – this is the most honourable lesson and it makes just people out of those who [wish to] learn it'.

Wreckers Coast of Northumberland J.M.W. Turner c.1834. Yale University Art Gallery (Yale University), New Haven, CT, USA

Notes

i. https://data.gmc-uk.org/gmcdata/home/#/reports/Fitness%20to%20Practise/Complaints/report.
ii. https://www.gmcdefencebarristers.co.uk/2021/12/case-closed-opportunities-to-resolve-your-gmc-fitness-to-practise-case-early/
iii. https://en.wikipedia.org/wiki/Icarus.
iv. https://dailystoic.com/4-stoic-virtues/.

President message

President-elect's message

Professor Roger Knaggs

Pain News
2022, Vol 20(4) 89–90

SAGE

Thank you to all of you who take the time to read *Pain News*. In preparing this message, I was reviewing some of the previous issues of *Pain News* and how it has evolved and matured over the years. The current editor, Dr Raj Munglani, has a vision for a publication that would stimulate and challenge us as well as provide us with updates on the day-to-day working of the Society.

As I mentioned in my previous column as President-elect, I would very much welcome suggestions from members about their thoughts on any topic relevant to the British Pain Society (BPS). I look forward to receiving your contributions directly to my in-box. Please email me directly at roger.knaggs@nottingham.ac.uk. I commit to reading and acknowledging every message that is sent to me.

In two linked editorials in a previous issue of *Pain News* (September 2020), several Council members including myself proposed that organisations providing essential and attractive resources (centred on the concept of a 'well' of provision of such resources) are likely to do better in the long term, in engaging and sustaining their members, than those organisations that create walls and artificial divisions between their members. These editorials are as relevant today as they were in the middle of the pandemic, and if you like to re-read them, they are freely available in the Members section of the website, as are all back issues of *Pain News*.

The BPS finds itself at crossroads, and it is an important time in its history. After many years of having our own permanent secretariat, our CEO Jenny Nicholas has been offered and accepted a new job opportunity at the Royal College of Nursing. We wish Jenny well as she moves forward in her career and thank her for her long years of unstinting service and commitment to the BPS.

Currently, we are in the process of appointing an external partner to help us with the day-to-day running of the Society. However, this time of change does provide us with the opportunity to review our strategic priorities and ways of working. You will hear more about these changes over the coming months.

This time of change provides us with an opportunity to recognise and review some of the great work going on within the Society. The BPS is fortunate to have 14 Special Interest Groups (SIGs). As suggested in the editorial in September 2020, these SIGs should be considered 'wells' within the Society – resources or wells of knowledge, expertise and support. They have the potential to allow groups of colleagues with a special interest in a part of our vast speciality to have more in-depth conversations and debate. During my term as President, I wish to raise both the member engagement with their SIGs and the profile and contributions of the SIGs within the BPS organisation.

President's message

I always look forward to reading the SIG reports submitted to Council to learn about what has been going on over the previous few months. However, wouldn't it be good if these could be shared more widely with other BPS members and by SIGs contributing articles to *Pain News* on a regular basis, informing the wider membership of webinars and events that they are arranging? It would also be good for all BPS members to read their annual reports in *Pain News* and to hear about their challenges and future vision with specific proposals about how these will be addressed. This will support our own development as professionals, allowing us to draw on the knowledge, skills and experience of our peers for the benefit of people living with pain.

There are some SIGs that have been dormant or inactive for several years. If this continues and there is no meaningful leadership or activity of a particular SIG, then considering our limited resources we may need to question the continuing existence of that particular SIG. We need vibrant and visionary SIGs to benefit us all.

The second part of the September 2020 editorial outlines a model for different ways of working and the importance of culture and structure. This requires leadership and we all should think about our role as leaders, whether locally, regionally or nationally, and how we can work together with a common goal to improve the lives of people living with pain.

As the BPS continues to evolve over the next few months, I wish to instigate the active (re)engagement with members and SIGs alike and to grow new members. In the meantime, I reiterate my comments in the last issue about contacting me directly with ideas or comments regarding anything pain-related or how the BPS can help you in your role, and also in turn how you can better support your professional colleagues and the Society.

Roger Knaggs.

Range of the Caucasus mountains. Ivan Aivazovsky, 1869

Article

A retrospective analysis of opioid prescriptions in patients referred to secondary chronic pain services

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Nofil Mulla *Pain Medicine Consultant, Bedfordshire Hospitals NHS Foundation Trust*

THE BRITISH PAIN SOCIETY
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SAGE

- What is already known on this topic: Chronic opioid use has increased worldwide in the past decade, leading to physical health and mental health problems, as well as societal harm.
- What this study adds: Opioid use in the chronic pain population is quantified by number, type and condition.
- How this study might affect research, practice or policy: Primary care physicians understandably resort to opioid prescribing in lieu of easy access to secondary pain services. A revised model of care delivery may help to address this problem.

Introduction

Opioid-based substances have been used by humans for medicinal and recreational use for over 8,000 years.[1] They are highly effective potent analgesics but also cause euphoria and patients can quickly develop tolerance due to receptor upregulation. They therefore are, and always have been, prone to recreational use and addiction.

In recent years, opioid prescribing has significantly increased. Prescribing for chronic pain has almost doubled between 1998 and 2018.[2] This has corresponded with a significant increase in opioid-related deaths in the United Kingdom (UK), known as the 'Opioid Epidemic' with up to five opioid-related deaths a day in 2019.[3] There is a similar picture globally, with the US opioid crisis claiming over 45,000 lives in a year[3] and being the subject of multiple popular culture books/TV serials.

The National Institute of Clinical Excellence (NICE)[4] has responded and issued clear guidance that opioid medications should not be prescribed for chronic pain. This is further supported by an expert working committee of the Pain Faculty at the Royal College of Anaesthetists that published a 'Best practice guideline' in March 2022, recommending judicious use of opioids in the perioperative setting.[5] Despite the guidance, chronic pain patients are often prescribed these powerful short-term medicines for chronic indications, leading to long-term prescription and opioid dependence.

Methods

We set out to analyse the opioid burden of patients presenting to a secondary care chronic pain service. A retrospective analysis of newly referred patients with a wide range of conditions was carried out. Four hundred patients were randomly selected from those who had their first chronic pain clinic appointment between February 2016 and February 2022.

Their electronic records were accessed for evidence of regular opioid prescription.

Results

Overall, 58% (n = 232) of patients presenting to secondary care services had a long-term opioid prescription at the point of referral. The majority (n = 190) of these patients were on 1 opioid; however, 36 were on 2 opioids and 6 on 3 long-term opioids (Chart 1).

The majority of opioid prescribing was for the weak opioid codeine; however, there was widespread prescribing of stronger opioids such as morphine, oxycodone and fentanyl (Table 1).

Chart 1. Number of opioid prescriptions per patient.

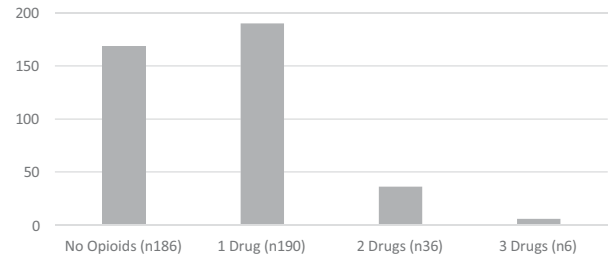

Table 1. Opioid prescription breakdown.

Opioid by type	N
Codeine	103
Morphine	55
Tramadol	37
Oxycodone	23
Fentanyl	18
Buprenorphine	13
Dihydrocodeine	7
Sevredol	2
Meptazinol	1
Tapentadol	1

When assessed by presenting complaint, there were differences in opioid-prescribing patterns (Table 2). Back pain made up most referrals to secondary pain services, and of these, 110 (65%) were on 1 or more long-term opioid. A similar picture was seen with other non-axial musculoskeletal pain, with 27 (64%) on long-term opioids. However, there was some variation depending on presenting complaints.

Fibromyalgia and headache patients had lower levels of opioid use (47% and 25%, respectively); however, there were still high number of patients who were prescribed these medications long term. Trigeminal neuralgia, post-herpetic neuralgia and abdominal pain patients had higher levels of opioid prescribing than the global figures (80%, 75% and 78%).

Table 2. Opioid usage by presenting condition.

Opioid by condition	N	%
Back pain (n = 168)		
No	58	34
Yes	110	66
Non-back MSK (n = 42)		
No	15	36
Yes	27	64
Fibromyalgia (n = 55)		
No	29	53
Yes	26	47
Trigeminal neuralgia (n = 5)		
No	1	20
Yes	4	80
Post-herpetic neuralgia (n = 4)		
No	1	25
Yes	3	75
Pelvic pain (n = 16)		
No	6	36
Yes	10	63
Headache (n = 8)		
No	6	75
Yes	2	25
Chest pain (n = 11)		
No	6	55
Yes	5	45
Cancer pain (n = 4)		
No	0	0
Yes	4	100
Abdominal pain (n = 18)		
No	4	22
Yes	14	78

Discussion

Opioid medications should be reserved only for acute pain in the non-specialist setting and should be viewed in the same way antibiotics are, with a start and end date, for a very clear acute indication, such as an injury. They should not be prescribed for chronic pain patients unless by specialist physicians, as is supported by various clinical guidelines (Box 1).

Box 1. Summary of opioid recommendations for various chronic pain conditions.

For trigeminal neuralgia – 'Do not offer any other drug treatment (apart from Carbamazepine – sic) unless advised to do so by a specialist'.[6]
For post-herpetic neuralgia – 'Tramadol may be considered if acute rescue therapy is required but should not be prescribed long term without specialist supervision'.[7]
For abdominal pain – 'A positive and clear diagnosis, including insight into the "wiring" of the central nervous pain system and the counterproductive effects of opioids'.[8]
For back pain – 'Do not offer opioids for managing chronic sciatica'.[9]
For chronic primary pain – 'Do not initiate (opioids) to manage chronic primary pain'.[4]

Our data demonstrated that there was a significant opioid burden among new chronic pain referrals. While encouragingly almost half (45%) of the opioid prescribing was for the weak opioid codeine, there were still many patients on stronger opioids. Over 10% of patients were prescribed two or more types of opioids for long-term use. Multiple guidelines have cautioned against the use of opioids by non-pain specialists in long-term conditions.

Certain conditions seem to be more affected than others. Musculoskeletal pain made up the majority of referrals to secondary pain services in our sample. This group had a high amount of opioid use (around 65%). As this group of patients is large in number, any non-opioid management that can be initiated by non-specialists should be researched, promoted and encouraged.

We observed that post-herpetic neuralgia, trigeminal neuralgia and chronic abdominal pain patients had higher levels of opioid prescribing than the general population of chronic pain patients. This is concerning as these conditions would not be managed effectively with long-term opioids and, in the case of abdominal pain in particular, could be made worse.

Fibromyalgia is a long-term multisystem health condition where the role for opioids is limited. The widespread number (47%) of fibromyalgia patients prescribed opioids by non-pain specialists is of significant concern.

Chronic pain conditions often result from a complex interaction of biopsychosocial factors, and long-term opioid usage is known to be associated with worsening mental health.[10,11] It may well be that some symptoms with which patients are presenting to secondary care are *as a result* of chronic opioids. While it is not clear entirely what is cause and effect, the psychological and physical dependency that results from long-term opioid use should not be underestimated.

Access to pain specialists can be challenging in the United Kingdom, with just 0.8 pain specialists per 100,000 patients reported in 2016.[12] This compares with 1 per 77,000 in New Zealand and Australia.[13] It is likely that non-specialists have turned to opioids to manage their patients' suffering, in lieu of easily accessible secondary pain services.

It is unlikely in a post-pandemic National Health Service that pain services are going to see a sudden increase in funding. Therefore, pain specialists must think 'outside the box' as to how access can be improved without an increase in resources. Pain specialists must educate colleagues outside of the speciality to the hazards of opioid prescribing. It is clear that clinical guidelines are ineffective at influencing prescribing habits in this context and there are many issues to deliberate.

Pain specialists have a duty to try and reduce the opioid burden in their patients *before* they attend clinic. Potential improvements are focused on pain specialists engaging with primary care in a more effective manner. Pain specialists could consider developing a rapid access pain service, utilising the MDT of secondary care services more efficiently. General practitioners (GPs) with a special interest in pain management should be encouraged and could be integrated into secondary care services to work dynamically to prevent inappropriate opioid prescribing in primary care. The potential role of restricted opioid prescribing in primary care needs to be considered, as does involvement of secondary pain services in General Practitioner Specialty training programmes.

Conclusion

Chronic pain sufferers have high opioid usage at the point of referral to secondary care, in conflict with established clinical guidance. Secondary pain services can be difficult to access for patients and clinicians alike. Wait times are long, referral pathways complex and patients can often be left for months or even years without help managing their pain. In these scenarios, it is unsurprising that non-pain specialists resort to prescribing opioids in an attempt to help ease their patients' suffering.

In view of the growing opioid crisis, pain medicine has a wider role in the healthcare sphere to improve the overall health and well-being of patients and not just improve pain. Healthcare professionals and service planners need to work collaboratively to mitigate the opioid epidemic. Pain physicians have a duty to think laterally as to how they can engage with patients and non-specialist clinicians to decrease chronic opioid prescribing in the community.

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Article

Opioid banning and pain acceptance

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THE BRITISH PAIN SOCIETY
EXPERTISE WHERE IT MATTERS

Pain News
2022, Vol 20(4) 95–97

SAGE

I have written before about the buzzword of 'Self-Management' either empowering sufferers or tidily hiding their suffering away from surveys or ever-increasing waiting list figures.

What worries me even more than this term is the theory of pain acceptance as promoted by the opioid-denying disciples. 'Accepting your pain' is something I often say myself to be honest. I tell people that you only begin to live with chronic pain when you accept it. I don't mean this to be used as an excuse to disregard chronic pain sufferers but rather that the sufferer begins to realise there is rarely a cure for chronic pain. While some people were wrongly prescribed over-strong medication and should be prescribed more suitable analgesia, those who need opiates must never be denied them through a blanket evangelical movement that says opiates are bad, bad, bad.

Any chronic pain sufferer has heard, or more likely been made aware by their clinicians, of the backlash against using opioids to treat chronic pain. This came about because of the 'opioid crisis' in America which put the blame on people in pain instead of the illegal drugs and pushers on the street.

Some patients are now forcibly being taken off their opiate medication because this theory has become accepted throughout the world and not just in America where the prescribing conditions are different. I find this particularly galling in Scotland because it's the Scottish Government's stated aim that clinical care must be 'person-centric'. 'Aye right!' as the sarcastic Scottish saying goes. The lack of control the Scottish Government has on the Scottish Health Boards is a matter for another debate.

Sadly, one way the forced withdrawal of opiates by clinicians has been sold to sufferers is through their erroneous understanding of 'pain acceptance'. Accepting your pain doesn't mean the pain disappears. It is still there with all its devastating side effects. This flawed understanding of pain acceptance means that patients are told to live with pain and the length of time a person is devastated by the pain is not considered relevant. Such is the concern of some to analgesia addiction that this perceived threat becomes paramount and the alleviation of pain given far less importance. It is clear that these people have never experienced chronic pain for anything more than the prescriptive 3 months. Chronic pain may be part of their job, but they do not live it. Living with it makes a massive difference to one's perception. They should really consider the following.

Chronic pain sufferers don't get a 'high' from taking opioids

Experienced clinicians, such as those in palliative care, know that taking painkillers because your body is in pain does not get you high. The only thing you experience is a dulling of the pain. The pain doesn't go away but becomes bearable. Only people who endure constant pain understand the difference. You are not addicted – you are relieved.

Thanks to my own free-thinking GP, I not only have slow-release opioids in my arsenal but also instant 20 mg oxycodone capsules. In all the years I've had these I haven't constantly increased the dosage as I would if I were addicted. I only take them for breakthrough pain. Yes, there are times I take more than usual, but that is because I am in a pain flare not because I want to get stoned. These breakthrough opioids get my pain down from ridiculously high levels to bearable levels. I now make a point of staying away from Pain Clinics as I know from listening to many Affa Sair members that I would be 'encouraged' to stop the opioids and use paracetamol and non-analgesia techniques to control the pain. This means obeying the derisory National Institute for Health and Care Excellence (NICE) guidelines which actually don't have any bearing in Scotland as we use the more acceptable SIGN guidelines.

I should also add at this point that I have tried to stop my own opioid medication under medical supervision. I gave it a damn good try over many months, but it was a disaster for me. The pain became so uncontrollable that I had no choice but to restart my oxycodone dosage. I didn't suffer any withdrawal effects at all – unlike when I stopped taking pregabalin. That's another story. For me, and many, many others, pregabalin is far more dangerous than opioids with disastrous consequences for users' mental health.

The work of Dame Cicely Saunders, who drove so much of modern thinking behind palliative care, should also be considered. Palliative care specialists are far more aware of how to control pain than other specialties. Her work in using opiates to 'kill the pain and not the patient' recognises opiates

have their use. 'But wait', I hear you cry, 'these people are dying – not living with chronic pain'. Well take it from me, decades of chronic pain makes death seem a pleasant alternative for many sufferers at some point in their lives. Why on earth should we be denied analgesia of any type which, when properly managed, can let us live again.

I am heartened to learn of a recent study of almost 200,000 opioid prescribed chronic pain sufferers who had no signs of being addicted to and abusing opioids. Three dosing strategies were studied: abrupt withdrawal, gradual tapering and continuation of the current stable dosage.

Those who were gradually tapered showed a higher incidence of opioid overdose or suicide events compared with those who continued taking a stable dosage. Mark LaRochelle, MD, Assistant Professor of Medicine, Boston University School of Medicine, Massachusetts, and colleagues wrote, 'This study identified a small absolute increase in risk of harms associated with opioid tapering compared with a stable opioid dosage. These results do not suggest that policies of mandatory dosage tapering for individuals receiving a stable long-term opioid dosage without evidence of opioid misuse will reduce short-term harm via suicide and overdose', they add.

The findings were published online on August 12 in *JAMA Network Open.* Referring to the now discredited Centers for Disease Control and Prevention (CDC) 2016 guideline, which recommended tapering opioid dosages if benefits no longer outweighed harms, the researchers went on to say that 'some health systems and US states enacted stringent dose limits that were applied with few exceptions, regardless of individual patients' risk of harms. But in reality, there have been increasing reports of patients experiencing adverse effects from forced opioid tapering'.

Pregabalin is the real danger

While undoubtedly helping reduce neuropathic pain, for me and for many thousands of others, gabapentinoids can do incredible damage to a person's ability to live a meaningful life. Yet these drugs are doled out with scarcely a murmur of a question on their long-term safety. There is hardly a whisper of this type of medication causing more cases of addiction than the maligned opioid. Where are the enraged politicians, focus groups and bandwagon-jumping evangelists on this one?

Back around 2019, I was placed in a 3-week programme at Scotland's National Residential Centre for Chronic Pain in Glasgow. One of the tenets of the programme was reducing medication, of course. In my case, I was more interested in reducing or stopping altogether my high dosage of pregabalin. I had been on this favoured medication for many years after my first visit to a Pain Clinic way back in the early 2000s. I started off on gabapentin, but the headaches were too difficult and so switched to pregabalin. I was really very happy with it as it did significantly reduce my neuropathic pain levels. And so it continued for many years, or so I thought.

You really need to ask my wife and family about the changes in me that robbed me of so many years of life and gave my wife, in particular, many years of a lonely unhappy life with a man slipping away into a dementia-like existence. My own recollections of those years are very sparse as I was unaware of what was going on around me. It was like living in a sea of mud.

I found it incredibly hard and tiring to even think straight. What hurt the most, when I was told about it later, was how I had changed from a hero-like uncle to someone who was no longer any fun or had no answers to the endless questions of a highly intelligent nephew. He told me once that it was like I had stopped being interested in anything around me. My wife, who knew I was ill before she married me, had the worst of it. There were no rows, or violence, just soul-destroying disinterest. She has often said since that those years were very lonely for her. I do have recollections of sitting in my chair, with perceived darkness enclosing me, struggling to even put words together for a simple sentence. My sharp intellect (I do have a high IQ level thanks to Asperger's Syndrome) just disappeared.

These days, my mother is in a care home with all the problems of dementia, and I recognise much of what she is going through now as the same as my time on a gabapentinoid. I was a miserable shell of a man compared to what I am now. There is no way I could have led Affa Sair to what it is now. I could never have written our website, articles and presentations I can now deliver reasonably easily, though never to my complete satisfaction – but that is another battle.

The withdrawal effects of pregabalin were terrible. In hindsight, winter was a bad time of year to do that anyway. My ever-attentive GP took me slowly through the tapering phase but even then there were times I was pleading with the receptionists on the end of the phone line for help that had me classed as an addict in withdrawal. I had a memorable frightening encounter with a man in a car park who so enraged me that I came within an inch of doing him physical harm. Such was my ferocious anger at him that I was bellowing incoherently at him and would have attacked him if he had been within reach. That was so out of character for me. I am a very placid, faint-hearted person in reality. When I calmed down

at home, I was terrified at my outburst but realised it was the withdrawal from pregabalin at fault. The thought of what might have happened scares me to this day. I remember my GP saying that they are told that these drugs are so helpful for chronic pain sufferers and have no reason to disbelieve what they are being told by pharmaceutical reps and fellow clinicians. He was really dismayed at what the pregabalin had done to me.

The way the effects had crept up on me led everyone to think it was just a progression of my many conditions and problems including an aorta-femoral bypass at 36, vascular disease, sleep apnoea, diabetes, hypertension, cholecystectomy, bowel resection, 3 TIAs, low testosterone levels, migraines and atrial fibrillation.

It took a good couple of years to be totally free of the effects of pregabalin, but I'm delighted to be able to do what I can do now. Such a huge change.

Chronic pain has severe side effects beyond agony

Accepting your pain doesn't mean the consequences of being in constant agony disappear. Chronic pain has many devastating side effects, way beyond the physical experience of pain, and to brush them aside with a blanket approach is negligent and dangerous for the sufferer.

Though not often spoken about, and completely denied by the DWP, one of the biggest side effects of trying to cope with chronic pain over many years is suicide. The suicide rate of chronic pain sufferers is roughly twice what it is for people without chronic pain. Once their medication is taken away and they can no longer live with the pain, ending it all is the only escape for some souls.

How can any opioid-denying clinician say that these sufferers were not helped by their opiates and just needed to accept their pain.

Pain acceptance is already part of chronic pain sufferers' lives

When you live with chronic pain year after year, you do eventually have to accept it is not going to go away. Searching vainly for a cure will do more damage to your mental well-being when your hopes of relief are constantly shattered. Once you learn to accept that living with pain is now your new life, you learn coping strategies to stop focusing on it. The very thing that the opioid banning brigade vigorously promotes is already a normal part of sufferers' lives. It is only made possible because strong pain-killing medication allows the user to reduce their pain to a liveable level.

I've written many times about strategies and techniques which help me cope with pain and distracts me from it. Methods such as reiki, meditation, massages, chiropractic treatment, acupuncture, TENS machines and my latest distraction technique – Painting by Numbers – allow me to live an acceptable life. Using and unavoidably spending a lot of money on these techniques are not the actions of people who don't accept their pain.

In conclusion, accepting your pain doesn't mean turning your back on medication nor should it be acceptable to make people suffer unnecessarily for a fashionable policy. The constant refrain of 'there is little evidence of opioids helping chronic pain' only means the research and opinion is all based on the harm they do rather than the good. 'Lack of evidence' frequently means a lack of study rather than a lack of efficacy. Clinicians and supporters of the 'opioids are bad' movement should remember that by taking an appropriate dose of opioids, users are relieved not addicted.

Article

THE BRITISH PAIN SOCIETY
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Pain News
2022, Vol 20(4) 98–103

SAGE

For the first time, a successful 'intervention' in primary care for chronic pain, showing long-term benefit: do guidelines help or hinder?

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Introduction

There continues to be a relative lack of high-quality, primary care–focused research on chronic pain.1

Current evidence relies heavily on experience collected in secondary care on cohorts of patients who have already been treated in primary care. The vast majority of acute and chronic problems are managed successfully by their general practitioners (GPs). It is when primary care treatment options have been exhausted that patients may be referred to secondary care. This is relevant to developed or established chronic pain in general and especially to patients with chronic back pain. Therefore, evidence currently available for chronic pain management is necessarily skewed. It omits the outcome data of the majority, which are the cohort managed in primary care by their GPs.

Chronic pain is common and affects between one-third and one-half of the population in the United Kingdom. It is one of the most common reasons for accessing healthcare and is the leading cause of disability globally.2 The vast majority of patients suffering from chronic pain have an element of musculoskeletal (MSK) pain, with 60%–90% being spinal (neck and back) and 20%–40% being osteoarthritis (OA) of major joints (hips, knees and shoulders).3 Back pain is one of the most common problems presenting to GPs.4

Yet, the National Institute for Health and Care Excellence (NICE) has recently changed guidelines on chronic pain and chronic back pain management. These guidelines are largely based on evidence that is of low quality, often small numbers and with ambiguous outcomes. They offer dwindling therapeutic options for GPs, and far from helping primary care clinicians, the guidelines have had the opposite effect of disempowering GPs, thus also impacting secondary care services with increasing waiting lists – impacting patient quality of life and increasing patient morbidity.

In 2015, the Surrey Heath Community Pain Service (SHCPS) tendered for, and won, the contract from the Surrey Heath Clinical Commissioning Group (CCG). The brief was to form a sustainable, multidisciplinary treatment model for chronic pain based in the primary care setting to provide a brief intervention management and treatment service to the Surrey Heath patients.

This service originally offered a successful MSK service (innovation prize 2006) and had expanded to also include the treatment of back pain. It was commissioned as a 'brief intervention model' offering an average of 12 appointments per patient. The SHCPS has treated 3,532 patients since its inception, in a catchment area of nearly 90,000 patients.

Although evidence-based medicine and NICE guidelines shape much of the treatment and management options offered

in this service, many of the treatments offered are also based on anecdotal, clinical expertise and patient choice on a case-by-case, individualised approach, as current guidelines fail to offer realistic choices. For example, recent guidelines call into question even basic analgesic choices including paracetamol, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), and non-pharmacological safe treatments such as transcutaneous electrical nerve stimulation (TENS).5

This article presents the outcome data from the brief intervention programme offered by the SHCPS with the objective of demonstrating that interventions based often on anecdotal evidence can offer outstanding results, not only at discharge but also in the long-term.

Method

The SHCPS receives referrals from nine GP practices looking after approximately 90,000 patients in the Surrey Heath catchment area. The referral criteria are the same as those for referral to secondary care chronic pain services. Patients need to be above 18 years and have pain that has been present for 12 weeks or more and not responded to first-line treatments, such as maximising simple analgesia, physiotherapy and with red flags having been excluded.

The referrals are sent on standardised forms that include medication, blood investigations and past medical history. These are then triaged for suitability within 48 hours of receipt (with occasional referrals being transferred to the community MSK clinic) and allocated appointments with the SHCPS ideally within 4–6 weeks.

The multidisciplinary team (MDT) includes primary care doctors with experience in MSK medicine and soft tissue injecting, physiotherapists with MSK experience, and psychologists with chronic disease management experience. In addition, our service includes sports therapists and an onsite pharmacist and pharmacy, supported by a cohesive administration team.

Pathway through the programme

The pathway through the brief intervention programme is flexible and takes into account patient choice. Prior to the programme, patients are encouraged to attend our introductory small group session on chronic pain and on what to expect on their journey through the service.

The programme starts with the 'new patient session' where patients are seen individually by all four clinicians of the MDT. This takes a full morning or afternoon lasting 3 hours. At the end of the session, patients will have seen the doctor who will assess symptoms and co-morbidities, review medication and discuss management options. In this first appointment, the doctor also initiates treatments, including pain-targeted soft tissue cortisone injections. The patient will also have had a subjective, functional and needs assessment with the physiotherapists and psychologist who also give advice and initiate rehabilitation. Following this, the team will debrief and recommend an individual treatment pathway.

Each patient has an average of 12 appointments in total. Following the new patient session, patients are offered follow-up appointments advised by the MDT. Patients also have input into their own treatment options, for example, some have been through chronic pain programmes in the past and have experienced what has worked before. Others are initially reluctant to participate in group sessions and would therefore be offered a 1:1 appointment to facilitate effective engagement in body and mind rehabilitation.

Data collection

To collect data for our study, at referral patients were asked to fill out a standardised questionnaire that included a pain score, where we measured how much pain interferes with seven daily activities including general activity, walking, work, mood, enjoyment of life, relations with others and sleep. Each was scored out of 10 and a mean was taken. They also filled out a EuroQoL, Patient Health Questionnaire–9 (PHQ-9) score and patient satisfaction survey. This same questionnaire was repeated at discharge and then again 3–5 years post-discharge.

Summary of results (see Appendix for full results data)

Just over 500 patients completed questionnaires at referral and discharge. A further 123 patients were able to be contacted to fully complete the post-discharge questionnaires. The discharge data showed statistically significant improvement across all outcome measures: pain Scores, EuroQoL and PHQ-9.

Patient satisfaction questionnaires at discharge were completed and 90% responded the programme was 'Very Good' or 'Excellent'. In all, 100% would recommend the service to family and friends.

Ninety-nine percent of patients were seen within 2–4 weeks of referral.

During the coronavirus pandemic, we had an opportunity to ask the question: Would the chronic pain symptoms relapse?

We contacted patients who were discharged from 2015–2017 consecutively to collect the same set of data to see whether these results were maintained and to see whether the treatment options offered to our patients had helped them not only in the clinic but also in the long-term. In total, 123 patients were successfully contacted. We found that not only had the positive results been maintained long-term (EuroQoL and PHQ-9), but they had also continued to improve when checked again post-discharge after 3–5 years (Pain Scores).

Discussion

Evidence-based medicine leads to standardised rather than excellent individualised care. (Michel Accad)

Chronic pain management is an example, 'par excellence', where standardised care is going to fail the majority.

Patients with chronic pain, primary or secondary, present with vastly diverse clinical symptoms, which can be complex with multimorbidity and polypharmacology – including the well-documented risks of opiate medication and potential for drug interactions and the burdens of side effects. In addition to this, chronic pain is recognised as a marker for increase in all-cause mortality,6 with 88% having significant co-morbidities, with cardiovascular disease, diabetes and depression being the most common.

Our primary objective is to improve function. Bearing in mind the improved health implication of increased exercise, activity and mobility, exercise is an integral part of rehabilitation of patients suffering from a variety of chronic pain conditions, and its effectiveness is well established. Exercise not only reduces pain perception but also has benefits for mental health such as mood elevation and reduction in stress and depression, often associated with chronic pain conditions.7,8

Our secondary objective is to reduce pain, thus facilitating and enabling effective engagement in our rehabilitation programmes, both physical and psychological, running concurrently. This often involves targeted joint and soft tissue cortisone injections at the outset. These are simple and safe interventions, typically available in sports injury and MSK services, without necessitating sedation or instrument guidance and are one of the major differences between the management pathway we offer and other chronic pain management services.

The SHCPS clinicians have been offering and providing joint and soft tissue cortisone injections from inception of the service. These soft tissue cortisone injections are mostly paraspinal lumbar and cervical MSK injections done in the clinic, at the site of maximum tenderness, as guided by our patients.

There are plenty of papers and books written, with evidence of effectiveness of joint and soft tissue steroid injections for almost every part of our anatomy and yet almost none for necks and backs! Silver's9 book '*Soft Tissue Injections*' has a chapter offering advice on injecting backs and necks up until the fifth edition. This chapter has been omitted from the latest sixth edition, under new authorship. Similarly, minor surgery courses that include joint and soft tissue injection skills for doctors and physiotherapists have omitted the spine module stating 'lack of evidence and for safety reasons'. However, acupuncture, considered very safe, is used for neck and back pain, using needles of varying lengths (commonly used needles being 25–40 mm).10 There are also studies and articles on Botox injections to paraspinal muscles and trigger points in the neck and back; these procedures are considered safe. With regard to cortisone injections in these areas of the body, there is a lack of evidence in the literature to support its efficacy, and this needs addressing. Current evidence for injection procedures for back pain focuses on medial branch blocks and radiofrequency denervation, epidurals, and facet joint injections which are secondary care procedures. In summary, soft tissue injections to the neck and back are safe, but the lack of evidence for efficacy does not mean they are not effective, merely that adequate data are not yet available.

In our experience, there is a necessity for management plans and treatment options to be individualised to adequately meet the needs of this heterogeneous cohort of patients and to ensure engagement in intervention programmes.

We have found that having soft tissue cortisone injections as a treatment option for chronic pain and back pain has had an important positive impact on the success of our outcomes. It is well known these injections have a limited therapeutic window of optimal pain relief. It is vital that physiotherapy and rehabilitation intervention is timed to coincide with the therapeutic window of optimal pain relief offered by cortisone injections, to facilitate maximal engagement in the programme.

Our initial data are preliminary; we would therefore welcome further trials on the benefit and efficacy of these simple and safe procedures including double-blind randomised controlled trials.

Conclusion

This is the first study to our knowledge that shows maintained improvement long-term following discharge from a chronic pain

management service. Our results show not only maintained improvement, but in our 'patient pain perception scores' that improvement continued many years after discharge.

It would seem to us in the latest guidelines for the management of chronic pain that NICE confuses 'having no studies showing effect' as the same as 'having studies showing no effect'. No evidence of benefit is not the same as evidence of no benefit.8 We need further trials on simple, safe treatment options that can be used in the community, where most of the patients suffering from chronic pain are managed. This study tries to address this gap.

Of particular note of our treatment options is that we have found targeted cortisone injections into the point of maximal tenderness to be particularly effective – especially into paraspinal lumbar and cervical MSK areas where, as we have mentioned above, 60%–90% of chronic pain occurs. We use triamcinolone acetonide with doses of 80–120 mg (Kenalog) with 100% safety record and no complications. There are two impacts we feel these injections have. There is the anti-inflammatory effect of the steroid that gives the patient a window of reduced pain in which to engage better in the physical and exercise therapies. However, there is another, often overlooked, effect of corticosteroids. Corticosteroids, such as triamcinolone acetonide, have long been used in the treatment of hypertrophic and keloid scars to decrease the size of the lesion. It is thought to work by the decrease in production of collagen, dissolution of insoluble collagen (collagenolysis) and an increased rate of apoptosis of fibroblast and inflammatory cells as well as possible effect on fibromatosis (e.g. regression of Duputren's nodules). Chronic pain patients often have a history of a single traumatic event that was the start of their pain. It is likely that this cohort of chronic pain patients' symptoms is due to inappropriate deposition of scar tissue. This scar tissue if in the wrong place could put pressure on nerves – what we call nerve entrapment syndromes. If we could 'dissolve' this scar tissue with the use of steroid injections and then prevent its re-deposition, through physiotherapy and exercise therapy, this could lead to the kind of dramatic and long-term improvement we have seen in our study. This would be a fascinating area of further research that we feel could make a huge difference to the future of chronic pain management.

We must note in our study that we report positive data not only at discharge but also in the 123 patients whose data were collected after 3–5 years post-discharge. These data were collected by calling patients and so could only be collected from those who answered the phone. It was unfortunate that the full 500 patients' data could not be used for this branch of the study. Due to this, we must recognise that although this is a good result we could not exclude selection bias, and so on. Further research into the management of chronic pain by primary care is urgently needed, particularly looking into how individualised care has impacted outcomes both at discharge and in the long-term.

We believe that access to simple targeted steroid injections alongside timely physiotherapy to enable a more effective engagement in rehabilitation and exercise is a key part of this model's success. Patients taking an active lead in the choice of therapeutic options is also key to promoting self-management and engagement in the programme, with access to many other different therapeutic options and techniques that our patients have found so valuable. This model of patient management allows for individualised care.

We recognise that patient-reported outcome measures are very subjective and as such are not ideal, and that some objective functional outcome measures would be better. However, pain is subjective, and currently there is no better method that we know of for measuring pain. These results are promising, in an area of medical management, that is, in general, falling short. There has been much frustration in primary care with the latest guidelines on chronic pain and back pain management. It should be accepted when considering future chronic pain management research and service design that guidelines are there to help and not hinder.

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Appendix

Full results

Effectiveness of brief intervention programme

Measure	N	Pre-treatment, mean (SD)	Discharge, mean (SD)	p value	p sig
Pain Score	505/463	6.1 (2.1)	3.9 (2.4)	26E–72	<0.05

1. Pain Score

Pre-referral 505 patients completed the Pain Score. The mean was 6.1 and the median 6, and the standard deviation was 2.1. At discharge, 463 patients completed the Pain Score. The mean was 3.9 and the median 4, and the standard deviation was 2.4. The difference between the means showed an improvement from 6.2 down to 4.0. A paired, two-tailed Student's t-test was performed on the data showing a p value of 2.6E–72. Therefore, a statistically significant improvement was seen in the Pain Score from referral to the clinic and at discharge ($p < 0.05$).

Measure	N	Pre-treatment, mean (SD)	Discharge, mean (SD)	p value	p sig
EuroQoL	503/465	48.9 (22.7)	67.3 (20.7)	3.2e-49	<0.05

2. EuroQoL

Pre-referral 503 patients completed the EuroQoL. The mean was 48.9 and the median 50. The standard deviation was 22.7. At discharge, 465 patients completed the EuroQoL. The mean was 67.3 and the median 70. The standard deviation was 20.7. The difference between the means showed an improvement in the EuroQoL scores from pre-referral to discharge from 47.8 to 66.7. A paired, two-tailed Student's t-test was performed on the data and the p value was calculated to be 3.2E–49. Therefore, a statistically significant improvement in the EuroQoL scores was seen from referral to the clinic and at discharge ($p < 0.05$).

Measure	N	Pre-treatment, mean (SD)	Discharge, mean (SD)	p value	p sig
PHQ-9	488/455	9.6 (7.6)	6.3 (7.5)	1.OE–13	<0.05

3. PHQ-9

Pre-referral 488 patients completed the PHQ-9 questionnaire. The mean was 9.6 and the median 8. The standard deviation was 7.6. At discharge, 455 patients completed the PHQ-9 questionnaire. The mean was 6.3 and the median 4. The standard deviation was 7.5. The difference between the means showed an improvement in the PHQ-9 score from 9.6 down to 6.3. A paired, two-tailed Student's t-test was performed on the data and the p value was calculated to be 1.0E–13. Therefore, a statistically significant improvement was seen in the PHQ-9 scores from referral to the clinic and at discharge ($p < 0.05$).

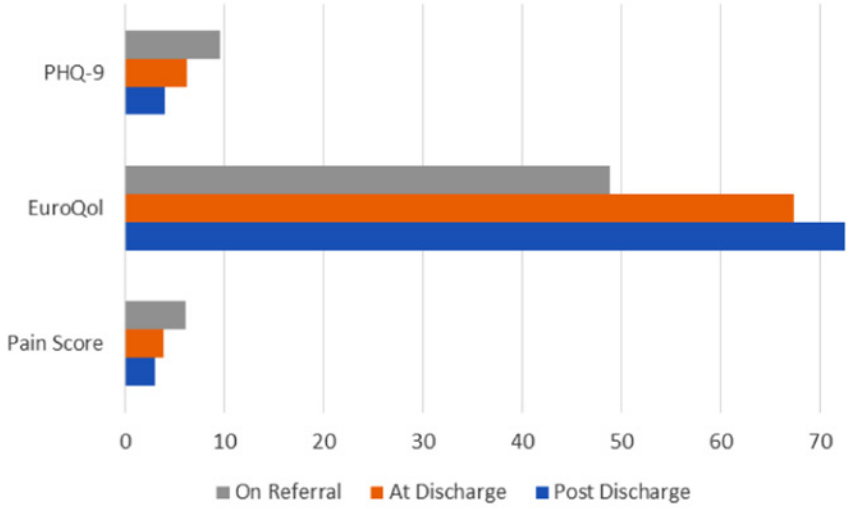
4. Patient satisfaction questionnaire

Patients were asked at discharge to rate the overall experience they had from their treatment at the chronic pain clinic. They were asked to rate the clinic as very poor, poor, good, very good and excellent. Ninety percent responded 'Very Good' or 'Excellent'.

No formal complaints from patients have been received. In all, 100% of the respondents said they would recommend the service to family and friends.

5. Time from referral to patient being seen in the clinic

Ninety-nine percent of patients were seen within 2–4 weeks of referral.



Are These Results Maintained Long-Term?

Pain Score

Post-discharge 123 patients completed the Pain Score. The mean was 2.99 and the median 3, and the standard deviation was 2.2. A paired, two-tailed Student's t-test was performed both looking for a difference from on referral to post-discharge and again looking for a difference at discharge and post-discharge. There was an improvement in the means from 6.1 at referral to 3.9 at discharge and then again to 2.99 post-discharge. The p value was 3.3E–24 comparing at referral to post-discharge showing a statistically significant improvement. The p value was 0.001 comparing at discharge to post-discharge showing a statistically significant improvement in pain scores that continued from at discharge to post-discharge ($p < 0.05$).

EuroQoL

Post-discharge 124 patients completed the EuroQoL. The mean was 72.6 and the median 73.5, and the standard deviation was 22.0. A paired, two-tailed Student's t-test was performed both looking for a difference from on referral to post-discharge and again looking for a difference at discharge and post-discharge. There was an improvement in the means from 47.8 at referral to 66.7 at discharge and then again to 72.6 post-discharge. The p value was 2.1E–14 comparing at referral to post-discharge showing a statistically significant improvement ($p < 0.05$). The p value was 0.083 comparing at discharge to post-discharge showing the difference was not statistically significant ($p > 0.05$), indicating a stable result from discharge to post-discharge.

PHQ-9

Post-discharge 124 patients completed the PHQ-9. The mean was 4.0 and the median 2, and the standard deviation was 4.8. A paired, two-tailed Student's t-test was performed both looking for a difference from on referral to post-discharge and again looking for a difference at discharge and post-discharge. There was an improvement in the means from 9.6 at referral to 6.3 at discharge and then again to 4.0 post-discharge. The p value was 1.8E–10 comparing at referral to post-discharge showing a statistically significant improvement ($p < 0.05$). The p value was 0.064 comparing at discharge to post-discharge showing the difference was not statistically significant ($p > 0.05$), indicating a stable result from discharge to post-discharge.

Article

Cannabis-based medicines for chronic pain – the state of current medical trials

Pain News
2022, Vol 20(4) 104–107

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Although it has been legal for some years to prescribe medical cannabis for patients with pain in several countries including Canada, many US states, Israel, Australia and many European countries, the United Kingdom has lagged behind most of the developed world in approving cannabis medicines for the National Health Service (NHS).

Since November 2018, it has been legal in the United Kingdom for specialist medical practitioners to prescribe cannabis-based medical products (CBMPs), although National Institute for Health and Care Excellence (NICE) guidelines from 2019 mean that in practice, CBMPs are only available on the NHS for a very small number of selected patients with three conditions: intractable nausea and vomiting due to chemotherapy, spasticity due to MS and intractable forms of childhood epilepsy.[1]

In the same guidelines, NICE concluded that there was insufficient evidence to recommend CBMPs for chronic pain and called for more data to help them evaluate the possibility of making CBMPs available on the NHS. In the meantime, CBMPs can be prescribed for chronic pain in the United Kingdom but only on a private basis, which makes the costs prohibitive for many people.

NICE have also been proactive in acknowledging the ineffectiveness of many conventional analgesics for chronic pain and osteoarthritis in 2021 and 2022,[1] further reducing the therapeutic options available for patients with pain.

At the same time, as NICE determined that CBMPs could not be prescribed on the NHS, a YouGov survey conducted on behalf of the Centre for Medical Cannabis revealed that 1.4 million people (2.8% of the population) in the United Kingdom were using illegal cannabis to treat chronic medical conditions including chronic pain and that more than 50% of these used cannabis daily.[2] This staggering figure reflects the significant unmet needs of patients living with chronic pain and the apparent disparity between what regulators decide is unsuitable for managing pain and what people with pain do in real life.

While double-blind randomised clinical controlled trials remain the gold standard for clinical evaluation and the main basis for recommendations by NICE, there are significant barriers to RCTs of CBMPs in chronic pain, not least because patient populations are notoriously heterogeneous and because CBMPs are also heterogeneous and are manufactured by small companies who cannot invest millions of pounds in clinical trials. In addition, RCTs of medications which must be very tightly controlled in terms of participants, dose, formulation, administration and outcome measures do not lend themselves to CBMP prescribing.

Since the endocannabinoid system (ECS) was discovered in the 1980s, a large evidence base has demonstrated that via the body's natural CB1 and CB2 cannabinoid receptors which are present on almost every tissue, the ECS plays a critical role in the regulation of many bodily systems including mood, appetite, homeostasis, sleep, pain, the endocrine system and inflammation. The ECS is very complex and poorly understood; however, it is known that two of the main plant or phytocannabinoids, cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) exert their effects via the ECS. Many other phytocannabinoids known as terpenes are also found in whole plant cannabis extracts and have their own

pharmacological effects although these are not well characterised. The so-called 'entourage' effect, whereby cannabinoids are thought to interact and produce a greater clinical effect than individual cannabinoid isolates, has been postulated.[3] This is also thought to be the mechanism by which CBD might help reduce the risk of unopposed THC-inducing anxiety.[4]

The duration of effects, both positive and adverse seen with CBMPs, depends on the formulation of the medicine and route of administration. These are usually either in the form of inhaled (vaporised) dried cannabis flower or via the sublingual or oral mucosal route as drops, tinctures or cannabis-infused oils. In addition, CBD preparations can be of different compositions depending on their method of preparation, typically so-called full-spectrum CBD which contains less than 0.3% THC, broad-spectrum CBD which contains no THC or CBD isolate which contains only CBD and no other terpenes. These preparations have different pharmaceutical effects.

Inhaled THC and CBD reach a peak plasma concentration at around 3–10 minutes, tapering off after 2–3 hours, whereas oral or sublingual formulations of CBD and THC typically take about 120 minutes to reach a maximum plasma level with the effects lasting 4–12 hours.[5] While inhaled CBMPs may therefore be less likely to produce adverse effects lasting many hours, they may also be less useful for long-lasting pain relief or an improvement in sleep quality.

The challenges involved in designing and conducting high-quality clinical trials of CBMPs that will deliver both meaningful real-world outcomes of value to patients and to provide the type of data required by NICE cannot be underestimated. Barriers to high-quality research include the heterogeneity of painful conditions, the many different formulations of cannabis products including synthetic cannabinoids, plant isolates and full-spectrum products, the doses and ratios of CBD and THC, the routes of administration of medical cannabis products, the numbers of patients available for recruitment and the duration of the clinical trials which are typically less than 6 months.[6]

NICE have, in 2022, agreed that good-quality real-world evidence, that is, data gathered from registries, insurance data and electronic health records, will be included in their future evaluations and they have produced a real-world evidence framework[1] to facilitate this process. Real-world UK registry evidence already suggests that CBMPs may be useful for patients with chronic pain, potentially helping significantly with pain, anxiety and sleep.[7,8]

The UK Medicines and Healthcare products Regulatory Agency (MHRA) have recently approved a 3-month feasibility study of a cannabis medicine in 100 patients with chronic non-cancer pain, aiming to provide ethical support for and data to inform a larger study on up to 5000 patients, which has been given MHRA conditional but not full approval. This study will be managed by LVL Health, a private medical cannabis prescribing clinic in London, and funded by Celadon Pharmaceuticals. If approved, the full CANPAIN study will run over 3 years and aims to match 5000 patients receiving an inhaled cannabis-based medicine with 5000 controls receiving standard care pain management via the NHS. Subjects will be recruited from a single population of patients with chronic non-cancer pain who are cannabis naïve and who will all receive the same formulation and dose of inhaled, whole flower cannabis via the same tamperproof vaporiser device. While hopefully this will generate additional useful data, it is already possible to predict the reaction of critics to any results, either positive or negative. Inhaled cannabis cannot be delivered blindly and will be expected to produce a strong placebo response. In order to make the trial financially possible, patients will have to pay a contribution towards their medicine. To satisfy MHRA safety and ethical concerns, the authors have had to carefully choose what might be a compromise CBMP that critics may argue does not reflect real-world experience. The CBMP chosen will be a short-acting balanced inhaled formulation containing 8% THC and 8% CBD. While this is a pragmatic approach that is likely to be safe and well-tolerated,[4] the product may not reflect the THC concentration that patients with pain typically seek illegally for pain (although this can vary significantly between strains) or the strength and formulations offered by medical cannabis prescribers which can contain THC levels of up to 22% or even higher. In addition, most patients prescribed medical cannabis for chronic pain will be offered both dried cannabis flower for rapid relief of symptoms and additional THC and CBD as infused oils, tinctures or capsules which have a much longer-lasting effect.

Worldwide there are approximately 20 other clinical trials of cannabis-based medicines in chronic pain conditions, currently recruiting or waiting to start recruiting. As expected, the paucity and quality of trials reflect the difficulties inherent in pain research, in general, and cannabis research, in particular. All cover a wide variety of chronic pain conditions, have very varied research methodology and use a diverse range of cannabis medications including CBD (full- and whole-spectrum) and THC alone and combined, both inhaled via vaporisation and for oral administration. Several of these are pilot studies or observational studies using as few as 26 participants.

In terms of randomised, placebo-controlled trials of cannabis-based medicines for chronic pain conditions, there are only four worthy of note. One of the most promising, at least in terms of methodology, is one based in Berlin, Germany, sponsored by Vertanical GmbH. This will recruit 808 participants with chronic low back pain into a randomised four-phase parallel assignment trial. All participants will take part in the first randomised double-blind placebo-controlled phase lasting up to 15 weeks, designed to assess the efficacy compared to placebo and safety of VER-01, an oral standardised cannabis extract administered via a syringe and containing 21 mg per gram THC. The optimum dose is titrated on a patient-by-patient basis and will not exceed 32.5 mg daily THC. Suitable patients who have completed the first phase will then enter other parallel phases, including two open-label treatment phases lasting up to 29 weeks designed to assess long-term safety and a randomised, double-blind placebo-controlled phase to check long-term efficacy, which will last until the first day of treatment failure.

Another interesting and well-designed ongoing study is the CANNFIB trial based in Frederiksberg University Hospital, Copenhagen. This is a randomised, double-blind, placebo-controlled, parallel group trial of 200 patients with fibromyalgia who will receive either an escalating dose of CBD up to 50 mg daily for 24 weeks or an identical-looking and tasting placebo tablet. There are multiple outcome measures including the change in pain intensity from the Fibromyalgia Impact Questionnaire, sleep duration and quality as well as quality of life and activities of daily living measures.

A smaller multi-centre, double-blinded, randomised, placebo-controlled study, based at NYU Langone Health, New York and sponsored by Orosa Health, aims to recruit 100 patients with knee osteoarthritis who will receive either CBD two to three times daily in the form or an orally disintegrating tablet at a dose of up to 150 mg daily, plus physiotherapy and home exercises, or a placebo disintegrating tablet plus physiotherapy and home exercises, for 84 days. Multiple outcome measures including pain levels, patient satisfaction and clinical outcomes will be assessed.

A similar randomised placebo-controlled study based at Weill Cornell Medicine, New York, sponsored by Nutra Pure, is recruiting 71 patients with temporomandibular arthralgia or myofascial pain to receive either 1 mL sublingual 20 mg/mL PURE CBD oil four times daily or placebo CBD oil derived from hemp for 11 weeks, and recording measures of pain and jaw function after set intervals up to 11 weeks.

One important clinical question addressed by several ongoing clinical trials is whether prescription CBMPs have an opioid-sparing effect. There is currently no good-quality clinical evidence for this Noori et al.[9] Researchers at the University of Colorado, Denver, are currently recruiting 150 patients with chronic pain who are opioid users to a 12-week double-blind, placebo-controlled phase 2 study with a parallel group study, designed to assess the tolerability and efficacy of full-spectrum CBD (containing less than 0.3% THC) and a broad-spectrum CBD (containing no THC) compared to a placebo control, to assess the effects on opioid use, anxiety and pain, sleep and cognitive function. At Maine Medical Centre and Massachusetts General Hospital, researchers are recruiting 250 patients with chronic non-cancer pain on high-dose chronic opioids to a 6-month randomised controlled trial comparing opioid use in morphine milligram equivalents daily, pain levels and a quality of life measure in patients offered their own choice of medical marijuana (the US term for CBMPs). This trial is aimed at reflecting real-world use, in addition to a behavioural support programme designed to support a voluntary taper of opioids, against a control group who will abstain from marijuana use and will participate in the behavioural intervention alone. The ReLeaf-E trial at the Montefiore Health System, sponsored by Albert Einstein College of Medicine, New York, also aims to ask the question of whether medical cannabis can reduce opioid use in adults with pain. They are recruiting a cohort of 352 patients with chronic pain, who are taking opioids and who are eligible for medical cannabis, to an observational study over 14 weeks. Participants will be prescribed cannabis in the form of a gel capsule containing one of three formulations; high THC:low CBD, an equal THC:CBD product or a low THC:high CBD product. Data sources will include questionnaires, urine samples and prescription-monitoring records.

At the University of Colorado Anschutz Medical Campus, Denver, the analgesic comparison of oxycodone and THC is being compared in a double-blind, placebo-controlled crossover study of 100 patients with chronic neck or back pain, by comparing either a single medium dose of vaporised THC compared to vaporised placebo plant material and both oxycodone and a placebo oxycodone capsule.

In a similar vein to the proposed CANPAIN study, a prospective observational study in Vancouver, British Colombia, sponsored by Canopy Growth Corporation, of 500 patients with chronic pain prescribed Spectrum Therapeutics cannabis products and included in the Canadian Pain Registry, has been completed recently and aims to provide real-world information regarding the prescription and use of Spectrum CBMPs in Canada, including types of product and doses prescribed as well as data on pain outcomes, sleep, daily functioning, quality of life and to assess changes in other medication doses including opioids over time. Another large Canadian

observational cohort study based at Toronto General Hospital aims to recruit 2000 patients with conditions including epilepsy, anxiety and chronic pain and to provide real-world evidence on patient-reported outcomes for approved patients prescribed TruTrace™ medical cannabis products.

Current clinical trials of cannabis-based medicines for chronic pain remain very scarce and generally of low quality. It is likely that the best way for NICE to be able to make a well-informed judgement on clinical policy regarding future NHS prescriptions for cannabis-based medicines for chronic pain will be for them to fulfil their intention to evaluate evidence from real-world data based on excellent quality clinical registry information, including validated assessments of health-related quality of life. I await the results of the CANPAIN feasibility study with interest.

Conflict of Interest

I am a medical cannabis prescriber at Sapphire Medical Clinics.

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Article

Placebos

THE BRITISH PAIN SOCIETY
EXPERTISE WHERE IT MATTERS

Pain News
2022, Vol 20(4) 108–112

SAGE

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> *a certain leaf, but there was a charm to go with the remedy; and if one uttered the charm at the moment of its application, the remedy made one perfectly well; but without the charm there was no efficacy in the leaf.*
>
> *Plato*

We would now call Plato's 'charm' a placebo. Placebos have been around for thousands of years and are the most widely studied treatments in the history of medicine. Every time your doctor tells you that the drug you take has been proved to work, they mean that it has been proved to work better than a placebo.[1] Every tax or insurance dollar that goes towards a treatment that is 'proved' to work is proved to work because it is (supposed to be) better than a placebo.

Despite their importance, doctors are not allowed to use placebos to help patients (at least, officially), and there are debates about whether we still need them in clinical trials. Yet the science of placebos has evolved to the point where our views should have – but have not – changed our prejudice against placebos in practice and the privileged position of placebo controls in clinical trials.

In this whistle-stop tour of the history of placebos, I will show what progress has been made and suggest where knowledge of placebos might go in the near future.

From pleasing prayers to pleasing treatments

The word 'placebo', as it is used in medicine, was introduced in Saint Jerome's 4th-century translation of the Bible into Latin. Verse 9 of Psalm 114 became: *placebo Domino in regione vivorum*. 'Placebo' means 'I will please', and the verse was then: 'I will please the Lord in the land of the living'.

Historians are keen to point out that his translation isn't quite correct. The Hebrew transliteration is *iset'halekh liphnay Adonai b'artzot hakhayim*, which means, 'I will walk before the Lord in the land of the living'. I think historians are making much ado about not much: why would the Lord want to walk with anyone who wasn't pleasing? Still, arguments about what placebos 'really' are continue.

At that time, and even today, the mourning family provided a feast for those who attended the funeral. Because of the free feast, distant relatives, and – this is the important point – people who pretended to be relatives attended the funeral singing 'placebo', just to get the food. This deceptive practice led Chaucer to write, 'Flatterers are the Devil's chaplains, always singing Placebo'.

Chaucer also named one of the characters in The Merchant's Tale, Placebo. The protagonist of the tale is Januarie. Januarie was a wealthy old knight who desired recreational sex with a younger woman called May. To legitimise his desire, he considers marrying her. Before making his decision, he consults his two friends Placebo and Justinius.

Placebo is keen to gain favour with the knight and approves of Januarie's plans to marry May. Justinius is more cautious, citing Seneca and Cato, who preached virtue and caution in selecting a wife.

After listening to them both, Januarie tells Justinius that he didn't give a damn about Seneca: he marries May. The theme of deception arises here, too, because Januarie is blind and does not catch May cheating on him.

In the 18th century, the term 'placebo' moved into the medical realm when it was used to describe a doctor. In his 1763 book, Dr Pierce describes a visit to his friend, a Lady who was ill in bed. He finds 'Dr Placebo' sitting at her bedside.[i]

Dr Placebo had impressive long curly hair, he was fashionable and he carefully prepared his medicine at the

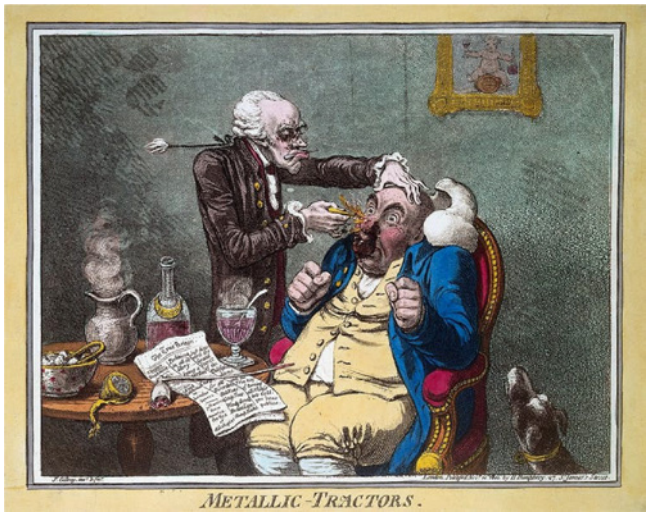
patient's bedside. When Dr Pierce asks his friend how she was doing, she replies: 'Pure and well, my old friend the Doctor has been just treating me with some of his good drops'. Pierce seems to imply that any positive effect Dr Placebo had was due to his great bedside manner, rather than the actual contents of the drops.

Eventually, the word 'placebo' started being used to describe treatments. The Scottish obstetrician William Smellie (in 1752) is the first person I'm aware of who uses the term 'placebo' to describe a medical treatment.[2] He wrote, 'it will be convenient to prescribe some innocent Placemus, that she may take between whiles, to beguile the time and please her imagination'. ('Placemus' is another form of the word 'placebo'.)

Placebos in clinical trials

Placebos were first used in clinical trials in the 18th century to debunk so-called quack cures, which is paradoxical because the so-called 'non-quack' cures at the time included bloodletting and feeding patients the undigested material from the intestines of an oriental goat. These were considered to be so effective that no trials were needed.

The earliest example I'm aware of where a placebo control was used is in a trial of 'Perkins tractors'. In the late 18th century, an American doctor called Elisha Perkins developed two metal rods he claimed conducted what he called pathogenic 'electric' fluid away from the body.



A quack treating a patient with Perkins Patent Tractors. James Gillray/Wikimedia Commons, CC BY.

He received the first medical patent issued under the Constitution of the United States for his device in 1796. The tractors were very popular, and even George Washington is said to have bought a set.

They reached Britain in 1799 and became popular in Bath, which was already a hub for healing because of its natural mineral waters and associated spa, which have been used since Roman times. Dr John Haygarth, however, thought tractors were bunk and proposed to test their effects in a trial. To do this, Haygarth made wooden tractors that were painted to appear identical to Perkins' metal tractors. But because they were made of wood, they could not conduct electricity.

In a series of 10 patients (5 treated with real, and 5 with fake tractors), the 'placebo' tractors worked as well as the real ones. Haygarth concluded that tractors didn't work. Interestingly, the trial did not show that the tractors did not benefit people, but merely that they did not produce their benefit via electricity. Haygarth himself admitted that the fake tractors worked very well. He attributed this to faith.

Other early examples of placebo controls tested the effects of homoeopathy tablets compared with bread pills. One of these early trials revealed that doing nothing was better than both homoeopathy and allopathic (standard) medicine.[3]

By the middle of the 20th century, placebo-controlled trials were prevalent enough for Henry Knowles Beecher to produce one of the earliest examples of a 'systematic review' that estimated how powerful placebo were. Beecher served in the United States Army during the Second World War. Working on the front line in southern Italy, supplies of morphine were running out, and Beecher reportedly saw something that surprised him. A nurse injected a wounded soldier with saltwater instead of morphine before an operation. The soldier thought it was real morphine and didn't appear to feel any pain.

After the war, Beecher reviewed 15 placebo-controlled trials of treatments for pain and a number of other ailments. The studies had 1,082 participants and found that, overall, 35% of the patients' symptoms were relieved by placebo alone. In 1955, he published his study in his famous article The Powerful Placebo.[4]

In the 1990s, researchers questioned Beecher's estimates, based on the fact that the people who got better after taking the placebos might have recovered even if they had not taken the placebo. In philosophy-speak, the possibly mistaken inference that the placebo caused the cure is called the *post hoc ergo propter hoc* (after, therefore because of) fallacy.

To test whether placebos really make people better, we have to compare people who take placebos with people who take no treatment at all. Danish medical researchers Asbjørn Hróbjartsson and Peter Gøtzsche did just that. They looked at three-armed trials that included active treatment, placebo control and untreated groups. Then they checked to see whether the placebo was better than doing nothing. They found a tiny placebo effect that they said could have been an artefact of bias. They concluded that 'there is little evidence that placebos, in general, have powerful clinical effects', and published their results in an article called Is the placebo powerless?, which contrasted directly with the title of Beecher's paper.

However, Hróbjartsson and Gøtzsche corrected Beecher's mistake only to introduce one of their own. They included anything labelled as a placebo in a trial for any condition. Such a comparison of apples and oranges is not legitimate. If we looked at the effect of any treatment for any condition and found a tiny average effect, we could not conclude that treatments were not effective. I exposed this error in a systematic review, and now it is widely accepted that just as some treatments are effective for some things but not everything, some placebos are effective for some things – especially pain.

Placebo surgery

Recently, placebo-controlled surgery trials have been used. In perhaps the most famous of these, American surgeon Bruce Moseley found 180 patients who had such severe knee pain that even the best drugs had failed to work. He gave half of them real arthroscopy and the other half placebo arthroscopy.[5]

Patients in the placebo arthroscopy group were given anaesthetics and a small incision was made in their knees, but there was no arthroscope, no repairing of damaged cartilage and no cleaning out of loose fragments of bone.

To keep the patients ignorant about which group they were in, the doctors and nurses talked through a real procedure even if they were performing the placebo procedure.

The fake surgery worked as well as the 'real' surgery. A review of over 50 placebo-controlled surgery trials found that placebo surgery was as good as the real surgery in more than half the trials.

Honest placebos

A placebo can work even if a patient does not believe it is a 'real' treatment.

In the first of the studies of open-label placebos (placebos that patients know are placebos) I know of, two Baltimore doctors by the names of Lee Park and Uno Covi gave open-label placebos to 15 neurotic patients.[6] They presented the placebo pills to the patients and said, 'Many people with your kind of condition have been helped by what are sometimes called sugar pills and we feel that a so-called sugar pill may help you, too'.

The patients took the placebos, and many of them got better after having the placebo – even though they knew it was a placebo. However, the patients were neurotic and a bit paranoid so they didn't believe the doctors. After the placebo made them better, they thought the doctors had lied and actually given them the real drug.

More recently, several high-quality studies confirm that open-label placebos can work.[7] These 'honest' placebos may work because patients have a conditioned response to an encounter with their doctor. Just like an arachnophobe's body can react negatively to a spider even if they know it's not poisonous, someone can react positively to treatment from a doctor even if they know the doctor is giving them a sugar pill.

The history of learning how placebos work

An early study investigating the inner pharmacology of placebo mechanisms is Jon Levine and Newton Gordon's 1978 study of 51 patients[ii] who had impacted molars extracted. All 51 patients had received a painkiller called mepivacaine for the surgical procedure. Then, at 3 and 4 hours after the surgery, the patients were given morphine, a placebo or naloxone. The patients didn't know which one they had received.

Naloxone is an opioid antagonist, which means that it stops drugs such as morphine and endorphins from producing their effects. It literally blocks the cell receptors, so it stops morphine (or endorphins) from docking onto those receptors. It's used to treat morphine overdose.

The researchers found that naloxone blocked the painkilling effect of placebos. This shows that placebos cause the release of painkilling endorphins. Since then, many experiments have confirmed these results. Hundreds of others have shown that placebo treatments affect the brain and body in several ways.[iii]

The main mechanisms by which placebos are believed to work are expectancy and conditioning.

In a comprehensive study published in 1999 of conditioning and expectancy mechanisms, Martina Amanzio and Fabrizio

Benedetti divided 229 participants into 12 groups. The groups were given a variety of drugs, were conditioned in a number of ways and were given different messages (to induce high or low expectancy). The study found that placebo effects were caused by both expectancy and conditioning.[8]

Despite the progress, some researchers argue – and I agree – that there is something mysterious about how placebos work. In a personal communication, Dan Moerman, a medical anthropologist and ethnobotanist, explained it better than I can:

> *We know from all the MRI people that it's easy enough to see what happens inside to the amygdala, or whatever other bit might be involved, but what moved the amygdala, well, that takes some work.*

History of placebo ethics

The accepted view in clinical practice is that placebos are not ethical because they require deception. This view has not yet fully accounted for the evidence that we don't need deception for placebos to work.

The history of the ethics of placebo controls is more complex. Now that we have many effective treatments, we can compare new treatments with proven therapies. Why would a patient agree to enrol in a trial comparing a new treatment with a placebo when they could enrol in a trial of a new treatment compared with a proven one?

Doctors who take part in such trials may be violating their ethical duty to help and avoid harm. The World Medical Association initially banned placebo-controlled trials where a proven therapy was available.[iv] Yet in 2010, they reversed this position and said we sometimes needed placebo-controlled trials, even if there is a proven therapy. They claimed there were 'scientific' reasons for doing this.

These so-called scientific reasons have been presented using obscure (to most people) concepts such as 'assay sensitivity' and 'absolute effect size'. In plain English, they boil down to two (mistaken) claims:

1. They say we can only trust placebo controls. This was true in the past. Historically, treatments like bloodletting and cocaine were used to treat a number of ailments yet were often harmful. Say we'd done a trial comparing bloodletting with cocaine for anxiety, and it turned out bloodletting was better than cocaine. We couldn't infer that bloodletting was effective: it could have been worse than a placebo or doing nothing. In these historical cases, it would have been better to compare those treatments against a placebo. But now, we have effective treatments that can be used as benchmarks. So if a new drug came along for treating anxiety, we could compare it with the proven effective treatment. If the new treatment proved to be at least as good as the old one, we could say it is effective.
2. They say only placebo controls provide a constant baseline. This is based on the mistaken view that placebo treatments are 'inert' and therefore have constant, invariable effects. This, too, is mistaken. In a systematic review of placebo pills in ulcer trials, the placebo response ranged from 0% (not having any effect) to 100% (complete cure).

As the arguments supporting placebo-controlled trials are being questioned, there is now a movement urging the World Medical Association to do another U-turn, back to its original position.

Whither placebo?

For centuries, the word 'placebo' was closely linked to deception and pleasing people. Recent studies of open-label placebos show that they need not be deceptive to work. Contrariwise, studies of placebos show that they are not inert or invariable and the basis for the current World Medical Association position has been undermined. The recent history of placebos seems to pave the way for more placebo treatments in clinical practice and fewer in clinical trials:

I acknowledge the James Lind Library, the writing of Ted Kaptchuk, Jeffrey Aronson, and the mentorship of Dan Moerman.

This article was published originally in The Conversation and republished with the permission of the author (https://theconversation.com/the-fascinating-story-of-placebos-and-why-doctors-should-use-them-more-often-149945). Dr Jeremy Howick has conducted studies about placebos, why we need unbiased experiments, and the evidence for self-healing and empathy.

He has degrees from Dartmouth College, the London School of Economics and the University of Oxford, and over 100 academic publications in top journals including the *British Medical Journal*, *Annals of Internal Medicine* and *The Lancet*. His research extends beyond academia and has influenced policy (he has collaborated with the National Institutes of Health in the United States, the National Institutes of Health Research in the United Kingdom and the Canadian Institutes of Health Research). He is also an experienced science communicator and he features

frequently in the media, including BBC News, Channel 5 (UK), ITV and many others. He appears regularly on the radio and television, and is an evidence expert for https://www.sciencemediacentre.org/. His latest book Doctor You explains these things in an understandable way (https://www.amazon.co.uk/Doctor-You-Revealing-science-self-healing/dp/1473654203).

Notes

i. https://www.jameslindlibrary.org/quoted-in-sutherland-a-attempts-to-revive-ancient-medical-doctrines/.
ii. Placebo Effects Understanding the Mechanisms in Health and Disease.
iii. Second Edition Fabrizio Benedetti. 25 November 2014. OUP.
iv. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

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Article

Managing your pain after surgery

Pain News
2022, Vol 20(4) 113

Felicia Cox *Nurse Consultant, Pain Management Services, Royal Brompton & Harefield Hospitals, Part of Guy's & St Thomas' NHS Foundation Trust; Chair Acute Pain SIG on behalf of the working party members*

It is well recognised that a proportion of patients continue to be prescribed and continue to take opioids prescribed for postoperative pain beyond the anticipated duration of need. Few inpatient pain services have the facility to review patients after hospital discharge (so-called transitional pain clinics), and primary care may supply repeat prescriptions without a clinical indication. This co-produced project promotes the safe use and timely weaning of opioids. It also aims to raise awareness of other significant harms associated with post-operative opioid use, namely opioid-induced ventilatory impairment, non-medical opioid use, opioid diversion and dependence (including in friends and family) and driving under the influence of prescription opioids. As well as addressing opioid use, this patient information resource also educates patients on other pain management strategies for their postoperative pain.

This was a joint project between the BPS and the Irish Pain Society with collaboration with a number of professional societies and groups. This information supplements the previously published *Understanding and Managing Pain After Surgery* (BPS 2018) and will be the first guidance that educates patients about safe postoperative opioid use, weaning and cessation. The main driver was the international opioid consensus document[1] which a number of the project group contributed to.

It is free to download and is available in a number of formats including a printer-ready proof and a Welsh language version. We would appreciate your patient feedback using the evaluation form. Further details including the evaluation form and document versions are available here _____

Reference

1. Levy N, Quinlan J, El-Boghdadly K, et al. An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients. *Anaesthesia* 2021; 76(4): 520–36.

**The BPS is setting up a new page to host all of the versions and the evaluation form.

End piece

The luncheon of the boating party

Pierre-Auguste Renoir

Pain News
2022, Vol 20(4) 114

1880–1881. The Phillips Collection, Washington, DC, USA

In this picture, Renoir portrays a much truer and more helpful idea of which we often need reminding: that despite the manifest failings of life and the world, it is still possible for us to have true and solid pleasures (Alain de Botton).[i]

Luncheon of the Boating Party (1881; French: Le déjeuner des canotiers) is a painting by French impressionist Pierre-Auguste Renoir. Included in the Seventh Impressionist Exhibition in 1882, it was identified as the best painting in the show by three critics. It was purchased from the artist by the dealer-patron Paul Durand-Ruel and bought in 1923 (for $125,000) from his son by industrialist Duncan Phillips, who spent a decade in pursuit of the work. It is now in The Phillips Collection in Washington, D.C. It shows a richness of form, a fluidity of brush stroke and a flickering light.

The painting, combining figures, still-life and landscape in one work, depicts a group of Renoir's friends relaxing on a balcony at the Maison Fournaise restaurant along the Seine river in Chatou, France. The painter and art patron, Gustave Caillebotte, is seated in the lower right. Renoir's future wife, Aline Charigot, is in the foreground playing with a small dog, an affenpinscher; she replaced an earlier woman who sat for the painting but with whom Renoir became annoyed. On the table is fruit and wine.

The diagonal of the railing serves to demarcate the two halves of the composition, one densely packed with figures, the other all but empty, save for the two figures of the proprietor's daughter Louise-Alphonsine Fournaise and her brother, Alphonse Fournaise, Jr, which are made prominent by this contrast. In this painting Renoir has captured a great deal of light. The main focus of light is coming from the large opening in the balcony, beside the large singleted man in the hat. The singlets of both men in the foreground and the tablecloth all work together to reflect this light and send it through the whole composition.

As he often did in his paintings, Renoir included several of his friends in Luncheon of the Boating Party. Identification of the sitters was made in 1912 by Julius Meier-Graefe.

At the Seventh Impressionist Exhibition in 1882, the painting generally received praise from critics. 'It is fresh and free without being too bawdy', wrote Paul de Charry in Le Pays, 10 March 1882. In La Vie Moderne (11 March 1882), Armand Silvestre wrote,

> *... one of the best things [Renoir] has painted ... There are bits of drawing that are completely remarkable, drawing- true drawing- that is a result of the juxtaposition of hues and not of line. It is one of the most beautiful pieces that this insurrectionist art by Independent artists has produced.*

Alternatively, Le Figaro published Albert Wolff's comment on 2 March 1882: 'If he had learned to draw, Renoir would have a very pretty picture ...'[ii]

Notes

i. https://www.sothebys.com/en/articles/for-the-love-of-art-alain-de-botton-on-art-as-therapy
ii. https://en.wikipedia.org/wiki/Luncheon_of_the_Boating_Party