From analgesia to addiction

A look at the growing problem of iatrogenic opiate addiction

The first recorded mention of the "milky juice of the poppy" was from the botanist Theophratus in the third century BC, and referred to a crude, early form of opium, used extensively with other plant derivatives in ancient medicinal concoctions. Celsus[1] and Galen both advocated for the use of the opium poppy before surgery, suggesting they were aware of its potential for pain relief. Further development over the next two millennia involved the purification of opium and its inclusion in various tinctures, but also its use in a social setting in order to induce euphoria and a state of relaxation in the user. In fact, it is widely believed that such greats as Wordsworth, Byron and Shakespeare were highly influenced by experiences under the influence of the painkiller laudanum which contained opium in liquid form. The English essayist Thomas de Quincey[2] describes opium as producing "for all anxieties a halcylon calm" in his 1821 autobiography entitled 'Confessions of an English Opium-Eater', which demonstrates the prestige that once accompanied opium addiction.

The prevailing attitudes appeared to change during the 1800s after Sertürner[1] isolated morphine from opium to produce a more standardised product which, when combined with the development of the hypodermic syringe[3], cemented opium's purpose as a medicine. Throughout the 19th and 20th centuries, researchers have worked to understand the pharmacology of opiates, creating different preparations and strengths of opiate-based medication for a number of clinical scenarios. The societally approved use of opiates, however, has remained medicinal hence there remains a social stigma associated with opiate addiction and laws worldwide restrict possession to reflect this[3].

The versatility of opiate analgesia means that it is currently indispensable as a medication, being used to manage both acute and chronic pain, with the latter involving an iterative process of fine tuning analgesic dosage. To standardise this fine tuning approach, the World Health Organisation (WHO) produced a 1986 guidance document[4], laying out a programme of progressive opiate dose titration. This took the form of the WHO Pain Ladder (Fig 1A),

and was initially used to treat adult cancer patients, but due to its success, the concept began to be applied to chronic non-cancer pain. Several modifications and revisions have been made to the steps involved (Fig 1B)[5], with the advent of new medications and novel methods of administration, but three decades on there is debate as to whether the guidance has remained relevant. Whilst some state that the addition of intermediate steps, and adjuvant drugs, has kept the ladder up to date, others argue that the harm caused by opiates in chronic non-cancer pain outweigh their benefits. Ballantyne et al published a commentary pointing out the decreased effectiveness of upward titrations of opiates over time, and highlighting the increased risk of addiction[6]. And in fact, the addictive potential of opiates may have been initially overlooked as cancer patients making up the ladder's original demographic were commonly palliative so addiction had less time to take hold. Now that the steps are being used in non-cancer pain, much like the lady who swallowed a spider to catch a fly, doctors are increasingly chasing long term tolerance with higher doses, contributing to addiction.

Figure 1A is adapted from the original WHO pain ladder (written in French). The choice of medication available in 1986 was limited, hence the categories are vague.

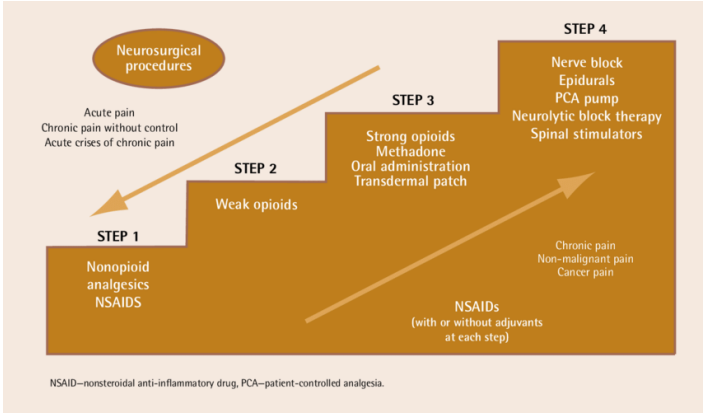

Figure 1B is an updated adapted version of the WHO pain ladder, proposed by Vargas-Schaffer. The medication options are more varied, allowing tailoring to the patient.

Data on the incidence of addiction to opiate analgesia was sparse through the early 2000s, partly because patients tend to present after a long period of addiction and so their numbers represent prevalence as opposed to incidence. The larger issue in establishing the scale of addiction however is one of terminology, with DSM-IV and ICD-9 classifications varying[7]. This is not helped by researchers frequently using *opiate misuse* and *addiction* both separately and interchangeably across different journals. One of the largest systemic reviews on the subject, conducted by Vowles et al, used recent consensus statements from the literature to define *opioid misuse* as 'use outwith the directed/prescribed pattern, regardless of the presence or absence of harm'.[8] The same authors describe *opioid addiction* as 'continued use with experience of, or demonstrated potential for, harm'. Through analysis of several papers, using these pre-agreed definitions, they showed that mean rates of opioid misuse range from 23.6% - 24.5%, whilst mean rates of addiction range from 8.8% to 9.8%[8]. With almost 1 in 10 chronic pain patients addicted to opiates, and approximately 30% of the American population experiencing chronic pain at some point in their lifetime, this represents a growing public health issue[9].

Cicero and Ellis performed an interesting study looking into differences between opiate addicts whose initial exposure was therapeutic versus illicit, and found that addiction potential did not differ vastly between therapeutic and non-therapeutic initial exposures. The striking similarity, from semi-structured interviews, was that regardless the source of the opiates, they provided the user with an initial euphoria which many pursued as a means to escape struggles in daily life[10]. This evidence points to there being innate factors driving development of addiction, and as our understanding of the pharmacology of opiates has increased, we have begun to elucidate some of them.

Endogenous opiate receptors, which bind endorphins and other naturally occurring opioids, also bind exogenous opiates such as morphine and its derivatives. Although they are expressed across the CNS, they are highly concentrated within the amygdala, nucleus accumbens (NAc), caudate putamen (CP) and ventral tegmental area (VTA), all of which contain GABA-minergic interneurons. When opioids bind to the μ-opioid receptors on GABA interneurons, they reduce the release of GABA, which in turn decreases their inhibitory effect on dopamine release[11]. As a result, opioid use causes dopamine to flood the mesolimbic pathways associated with the VTA, which have been conserved through evolution to reward beneficial actions such as food seeking behaviour. This rapid increase in dopamine produces a feeling of reward, reinforcing drug taking and drug seeking behaviour, thereby driving addiction. Physical dependence, sometimes misattributed exclusively to addiction, occurs in all patients taking opioids and will stop, on cessation of opiate therapy, at a point dependant on duration and dosage of treatment. Addiction takes months to occur, and is driven by mesolimbic activation in response to external stimuli such as alcohol, gambling or opioids, be they illicit or therapeutic.

Although addiction has a neurological basis, there are variable rates of addiction amongst populations of patients on opiate therapy for chronic pain, which is thought to represent the influence of genetic and environmental risk factors. As far back as the 1990s, researchers had shown that patients with close relatives who suffered from opioid use disorders are 10 times more likely to develop similar issues. This shows that there is a 'transmission effect' in opioid addiction[12], but further research was required to tease out the environmental and genetic components to this phenomenon. Cadoret et al studied a population of adoptees whose biological parents had substance misuse disorders and a control population[13]. They found that regardless of the environment of upbringing, there was an increased risk of substance misuse where parents had similar issues, meaning that there must be a genetic element to transmission. Recent advances in research techniques, such as genome sequencing, have identified candidate genes which mutate in addiction and most of these are involved in dopamine signalling.

For example, single nucleotide polymorphisms (SNP) in the A_1 allele of the D2 dopamine receptor gene have been shown to predict the success of methadone maintenance treatment (MMT) programmes in opiate addicts. On sequencing the genome of those successful after 1 year of MMT, researchers found the same SNP in 9.3% of patients, whereas the percentage was significantly higher (22.7%) in unsuccessful patients[14]. Authors of a recent review into the genetic basis for addiction use this as evidence that mutations, commonly in dopamine receptor genes, lead to increased impulsivity and risk of addiction[11]. Presumably these mutations, when passed from parent to child, transmit a genetic predisposition to develop problems with substance misuse and abuse.

Research into the genetics of addiction is useful to build a picture of how inherited and environmental factors interact in mental illness, but it simply is not feasible to sequence the genome of every patient before moving them up the WHO pain ladder. Prescribers therefore need to find an easier way to identify those at risk of addiction, before dispensing opiates, and environmental factors are very useful for this purpose. Volkow and McLellan have drawn on a number of recent research papers in order to compose a list of easily identifiable factors associated with a risk of opiate addiction[9] (Table 1). These are useful in determining addiction risk thorough an easy and quick conversation with the patient, hence their inclusion in various opiate addiction risk screening tools. The Current Opioid Misuse Measure (COMM)[15] and Screener and Opioid Assessment for Patients with Pain (SOAPP) are two commonly used tools for just such a purpose. Validation of COMM in chronic pain patients involved urine sampling for toxicology as well as completion of the 42-item Prescription Drug Use Questionnaire (PDUQ), considered one of the most well-developed tools at the time. The above measures allowed subjects to be classified on the Aberrant Drug Behaviour Index, before having all the assessed measures compared to scores from completing the COMM screening tool. On comparing patients' COMM scores to their Aberrant Drug Behaviour category, authors were able to show a reliability coefficient of 0.83. This was strong enough to demonstrate that COMM, although it is shorter than the PDUQ, is as reliable a tool for detection of current aberrant opiate use[15].
As is the case with most screening tools, researchers have tried to shorten both COMM and SOAPP whilst still retaining their predictive value in order to meet medical staff's increasing time constraints. Researchers did exactly this with the revised SOAPP tool, reducing the original 14 items to 8 (SOAPP-8), whilst maintaining high levels of sensitivity and specificity[16]. This is advantageous to primary care prescribers as they now save valuable consultation time, whilst still gaining a good impression of a patient's risk of developing opiate addiction. Further to this, there is now the option to use lengthier tools, with higher sensitivity/specificity, at initial visits but shorter tools during follow-up consultations to objectively track addictive behaviours.

Table 3. Factors Associated with the Risk of Opioid Overdose or Addiction.

Factor	Risk
Medication-related	
Daily dose >100 MME*	Overdose,[8] addiction[8]
Long-acting or extended-release formulation (e.g., methadone, fentanyl patch)	Overdose[14,41]
Combination of opioids with benzodiazepines	Overdose[42]
Long-term opioid use (>3 mo)†	Overdose,[43] addiction[44]
Period shortly after initiation of long-acting or extended-release formulation (<2 wk)	Overdose[45]
Patient-related	
Age >65 yr	Overdose[46]
Sleep-disordered breathing‡	Overdose[47]
Renal or hepatic impairment§	Overdose[48]
Depression	Overdose, addiction[49]
Substance-use disorder (including alcohol)	Overdose,[50] addiction[49]
History of overdose	Overdose[51]
Adolescence	Addiction[52]

* The risk of opioid overdose increases in a dose–response manner at opioid doses of more than 20 morphine milligram equivalents (MME).
† Although addiction is associated with long-term but not short-term opioid use, the prescription of a higher quantity of opioids than is needed for acute pain contributes substantially to the availability of opioids for diversion and abuse.
‡ Sleep-disordered breathing refers to conditions that manifest as abnormal breathing patterns during sleep and includes obstructive sleep apnea and central sleep apnea.[53]
§ Patients with these disorders are at increased risk because the disposition of various opioid drugs is affected by hepatic and renal impairments, which reduce drug clearance and increase bioavailability.[54-56]

Table 1 shows the environmental and lifestyle factors associated with increased risk of addiction. Adapted from Volkow and McLellan's 2016 paper.

From the above research, it is clear that opioid misuse and addiction are conditions with an aetiology centred partly in a patient's genetics, but shaped greatly by environmental factors and their co-morbid psychiatric state. This does not, however, stop opioids from being a useful rung of the pain ladder which often represents the cornerstone of first-line prescription in chronic pain patients. So how can clinicians who prescribe opioids do so in a safe manner in order to reap their benefits whilst avoiding the deleterious side effects? Prescription of long term opiates for those with chronic pain occurs commonly in general practice within the UK, but according to a new study into the practice, patients are being over prescribed opiates in more than a quarter of cases[17]. Combined with evidence of prescription opiates having as much addictive potential as illicit sources, this suggests that we need to increase prescriber education on the subject. An opinion piece in the New England Journal of Medicine echoes this, with the author stating that a balance can only be struck in prescription of opiates through rigorous education from the level of medical student to consultant[18]. Such a scheme has been set up in the US, whereby manufacturers of extended-release and long-acting opiates are mandated to provide voluntary opt-in education for prescribers. There is not enough evidence to accurately determine the effect of this scheme, but preliminary evaluation suggests that it has led to a culture of safer prescribing within the States. In the UK, anaesthetists are so commonly involved in the control of long term pain that the Royal College of Anaesthetists have released a similar resource called *Opioids Aware*[19]. The initial step in the prescription of opioids, they suggest, should involve an "Opioid Trial" which is a period of around 2 weeks in which the patient is prescribed the opiate. They are asked to keep a diary of daily opioid doses, twice daily pain score, sleep quality and levels of activity/functionality for the entirety of the trial. Both the patient and the physician can then build a more objective picture of the daily effects of short term opiate therapy before planning any future prescriptions. The guidance goes on to further discuss the applicability of a variety of choices in opiate drug, as well as route of administration, for different types of pain in patients[19].

Dosage is, however, a controversial subject, especially as long term opiate use leads to tolerance, hence patients require larger and larger doses to achieve therapeutic effect from their medication[11]. Interestingly, Higgins et al found that addiction occurred less in patients who received longer courses of opiates at higher doses than those who were dosed according to guidelines. This was an incidental finding from the team's attempt to estimate incidence of iatrogenic opiate addiction across several studies, but they used it to postulate a theory of 'Pseudo-Addiction'[7]. The suggestion is that patients displaying signs of addiction, such as use of opiates more frequently than prescribed, or increasing their dose without medical advice, were doing so because they were inadequately analgised. Careful scrutiny of the results is required, however, and it would seem they are better interpreted in support of good dialogue between prescriber and patient. It could be suggested that this Pseudo-Addiction would not occur if an opiate trial had been undertaken and the patient had been given an appropriate, but still guideline based dosage. The *Opiate Aware* guidelines therefore represent an excellent resource for prescribers who do not possess the pain management knowledge of an anaesthetist. Hence they should be used by anyone responsible for opioid prescription in the medium to long-term until patients can attend a dedicated pain clinic.

The above evidence epidemiological data shows that regardless of the use of screening tests and safe prescription, in line with current guidelines, patients can slip through the net. It is

therefore pertinent to finish by discussing some recent research into management of opiate addiction. Two important Cochrane reviews on opiate detoxification, using opiate replacement as well as psychosocial intervention, have shown that psychosocial treatments are a beneficial addition to the process. Buprenorphine and tapered doses of methadone appeared to have similar efficacy in detoxifying opiate addicted patients, although withdrawal symptoms appear to resolve more rapidly with buprenorphine[20]. The addition of psychotherapy to the pharmacological detox approach decreased the rates of dropout for the programme (RR 0.71), as well as decreasing the risk of opiate use at follow up (RR 0.66)[21]. With regards to the structure of psychological approaches, Garland and Black discuss the use of mindfulness in tackling iatrogenic opiate addiction, by working to decrease the patient's attentional bias towards drug related cues. This bias normally leads to habitual behavioural responses to drug cues, which cements the addiction, and it is through a programme of mindfulness that researchers helped patients to break these associations and thereby reduce opiate cravings[22].

Societal perspectives on opiates has changed, and an addiction once considered sophisticated has more recently been stigmatised. Use of opiates has persisted in medicine, but we have recently started to understand that addiction is rooted in genetics with an environmental element. Development of screening tools has helped prescribers to identify patients at risk of addiction, and guidance has been developed in an attempt to govern prescription patterns. Still, however, more and more patients appear to be progressing through opiate misuse to addiction and so researchers are working to develop detoxification and rehabilitation programmes. The message, from across the literature, is that opiates are useful in management of chronic pain, but that prescribing opiates in line with national guidance is vital in striking a balance between therapeutic benefit and harm.

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