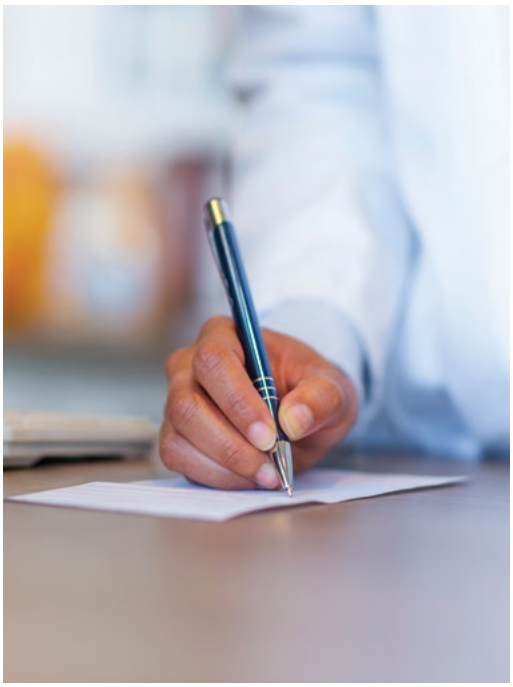
Pharmaceutical pitfalls in treating patients with advanced cancer



Taylan Gurgenci, Jones Chen, Benjamin Jull, Claire Stokes, Dominic Eu, Phillip Good

Background
This paper presents a collection of important topics that are not related to the other Focus papers in this *AJGP* issue on palliative care but are nevertheless important for clinical practice.

Objective
This article reviews the safe use of fentanyl, the proper use of buprenorphine and oxycodone–naloxone, and the potential pitfalls of equianalgesic tables.

Discussion
Sublingual and transdermal fentanyl are contraindicated in patients who are opioid-naïve. Opioid-naïve has a strict definition. Buprenorphine does not reduce the efficacy of other analgesics. Equianalgesic tables should not be followed blindly – they have many shortcomings, even if they are the best guidance we have. The benefit of combined oxycodone–naloxone products is modest in patients receiving palliative care in whom there is a higher risk of therapeutic failure and adverse effects. In summary, these are clinical topics that frequently arise when specialist input is sought but are not directly addressed in most clinical articles.

THIS PAPER is one in a series on palliative care written exclusively for *AJGP*. In mapping out the series, there were some topics that were too narrow to merit a full article but were nevertheless important, namely:

1. Things to know when prescribing fentanyl disintegrating oral tablets.
2. Prescribing fentanyl patches and troubleshooting problems.
3. Common questions about buprenorphine.
4. Equianalgesic tables and their many limitations.
5. Treatment failure with oxycodone/naloxone-modified release products.

These topics frequently occur for those in training and those working in general practice and general medicine. They often require consultation and collaboration with palliative medicine specialists. References have been chosen specifically for their teaching or historical value.

Things to know when prescribing fentanyl disintegrating oral tablets

Orally disintegrating fentanyl tablets are administered sublingually. The Pharmaceutical Benefits Scheme (PBS) subsidises the cost when prescribed for breakthrough pain in patients with cancer who are receiving palliative care. Fentanyl disintegrating tablets are contraindicated in patients who are not opioid tolerant.[1] Opioid tolerance is specifically defined here as 'taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 µg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day … or an equianalgesic dose of another opioid daily for a week or longer'.[1]

Tablets are available in six strengths: 100, 200, 300, 400, 600 and 800 µgrams. There is no relationship between an effective fentanyl disintegrating oral tablet dose and background opioid use.[2] Put plainly, some patients who take a lot of background opioid get pain relief on the starting dose of a fentanyl disintegrating oral tablet, and some patients on a more modest background opioid dose need higher doses of a fentanyl disintegrating oral tablet. Fentanyl disintegrating oral tablet doses are not interchangeable with other oromucosal options.

What follows from this is that there exists a mandatory dose titration protocol detailed in the product information as well as in commonly used resources like the Therapeutic Guidelines and Australian Medicines Handbook. There are some specialists who argue titration is not needed for short-acting fentanyl products, though the authors of this paper do not agree.[3]

Even if these arguments have scientific basis, from a clinical and legal perspective, it is recommended to comply with the principles of dose titration provided with the product information. Those who hold to the no-need-to-titrate view are in the minority.

The authors of this paper use fentanyl orally disintegrating tablets for severe incident pain that comes on very quickly and is not predictably associated with any activity. If the pain always happens in certain situations (eg taking a shower), we would try prescribing some other short-acting opioid (morphine, oxycodone) 20–30 minutes prior to the activity rather than using fentanyl. The advantage of fentanyl to treat this type of unpredictable pain is that the time to analgesia is faster than the PBS-subsidised alternatives. The disadvantages include cost, titration phase being off-putting for some patients, and a higher risk of accidental overdose when family members administer fentanyl to their loved ones.[4]

Prescribing fentanyl patches and troubleshooting problems

Fentanyl patches come in 12, 25, 50, 75 and 100 µg per hour strengths. They are contraindicated in patients who are not opioid tolerant (defined in the previous section).[5] Lacking renally cleared active metabolites, fentanyl can be prescribed to treat patients with renal impairment including those who have dialysis dependence.[6] Patches should be changed every three days. Pain worsens on the third day for up to one-fifth of patients, and this is best managed by changing the patch every second day instead of increasing the dose.[7] In such cases, the PBS will grant authority for the prescription of a box of 15 patches.

There are anecdotal reports that increasing fentanyl patch doses sometimes fails to improve pain in patients with cachexia.[8] There is no rigorous prospective study supporting this, but that does not mean it is not true. If increasing fentanyl patch doses have not helped, it might be safest to convert to an oral medication based on the lower dose (not the increased dose). When converting from a fentanyl patch to twice-daily modified release oral opioids, healthcare practitioners should give the first dose 8–12 hours after removing the patch. If converting to an infusion, the patient should start the infusion 6–8 hours after removing the patch. Alternatively, the patient can add an additional opioid dose via an infusion while keeping the patch on. Speaking to a palliative specialist might be worthwhile if the doses are high.

A common question about buprenorphine

Buprenorphine is a partial agonist at the mu-opioid receptor.[9] Its affinity is greater than morphine and other commonly prescribed opioids. This pair of facts leads some to ask, 'If buprenorphine is a partial agonist that has more affinity than morphine (or most other opioids), won't it blunt the analgesic effect of breakthrough doses of other opioids?'. The following discussion gets a bit technical, so we will answer this question first: no, buprenorphine will not block the analgesic effect of other opioids. You can use other opioids with buprenorphine.

The question is premised on misconceptions. The first is to think a partial agonist will necessarily be less clinically effective than a full agonist at usual analgesic doses. This is not borne out in the literature, with buprenorphine showing similar or greater analgesic efficacy than full mu-opioid receptor agonists.[9] If a very high proportion of mu-opioid receptors were saturated, then this could be the case; this is rarely a practical concern.

Conceptually prior to this is to mistake what a partial agonist is. A partial agonist is defined in comparison with some reference agonist.[10] Morphine can be defined as a partial agonist in some settings (ie with reference to opioids used in experimental but not clinical settings). It is wrong to always equate partial agonism with poor analgesia.[10]

This is the theoretical basis for the claim that buprenorphine will not blunt the analgesic effect of other opioids given for breakthrough pain. To suggest it would: (a) assume complete saturation of mu-opioid receptors by the background buprenorphine; and (b) equate partial agonism with partial clinical efficacy. Clinical trials show buprenorphine will not impair analgesia from other opioids. Other opioids will still be effective for breakthrough pain. The reverse is also true; short-acting buprenorphine will not paradoxically worsen pain for patients on some other long-acting opioid such as morphine.[11,12]

More practically, buprenorphine patches are changed weekly. The available doses range from 5 to 40 µg/hour. The starting dose has an oral morphine equivalent of approximately 10 mg/day, and these patches are useful as a background opioid option for patients who are opioid-naïve.

Equianalgesic tables and their limitations

Patients with advanced cancer are often changed from one opioid to another; this is called 'opioid rotation'. The variation in dose conversion might be surprising given how common this practice is.[13] Smartphone applications based on the traditional equianalgesic tables exist; though helpful, they use should be used with caution, as they can give the appearance of certainty in uncertain situations.

This section does not apply to methadone rotation, which is approached differently and not considered here.

Equianalgesic tables are generated from data obtained from mostly single-dose studies in different patient populations. They do not account for each patient's unique physiology and interacting medications. Bidirectionality is assumed. Refer to the study and textbook by McPherson for more details.[14,15]

Because there is some uncertainty as to what the target dose should be, practice errs on the side of underdosing when rotating to a different opioid. Reducing the calculated background dose by 25–50% means that the uncertainty is less likely to cause potentially fatal opioid toxicity. The corollary is that there is a risk of temporarily worsened pain. This is managed by the liberal use of short-acting breakthrough analgesia with each dose 10–20% of the target dose (except for fentanyl, as previously discussed). Practitioners should note whether their conversion resource accounts for the dose reduction (eg the Donner conversion table between transdermal fentanyl and oral morphine accounts for dose reduction).[14,15] Where doses are high, it is always worthwhile checking the target dose with a pharmacist or colleague for confirmation.

The message we would want readers to take away is that there is a potential margin of error when using equianalgesic tables or smartphone applications. This is especially

the case when high doses of opioids are being used. Despite these limitations, it is helpful to note what principles are used for each specific conversion.

Treatment failure with oxycodone–naloxone modified-release tablets

Combined oxycodone–naloxone products are marketed as providing background pain relief with decreased constipation. Oxycodone is an opioid, and naloxone is an opioid receptor antagonist. Naloxone is used as an antidote in opioid toxicity. In the case of oxycodone–naloxone, the naloxone part acts locally in the intestine to prevent opioid-induced constipation. It does not block pain relief because there is near-complete first pass metabolism in healthy individuals.[16]

Massive hepatic metastatic disease; portal flow reversal because of neoplastic compression, thrombus or cirrhosis; and other conditions can all lead to variable naloxone bioavailability.[17,18] When this happens, naloxone will block the pain relief provided by oxycodone. Recognising this can take time, and the natural reaction is to change oxycodone–naloxone to an alternative. It can be difficult to decide what dose of a different medication to rotate to. Equianalgesic tables have many limitations, as we have described. This opioid rotation has the added difficulty of an unknown amount of systemic naloxone reducing the effective dose of the oxycodone component in oxycodone–naloxone, underscoring the importance of noting limitations to equianalgesic dose tables (refer to the 'Equianalgesic tables and their limitations' section). Patients should be encouraged to take aperients even when on oxycodone–naloxone, but they need to be informed that constipation could theoretically worsen when rotating from oxycodone–naloxone to a different opioid.

Conversely, the benefit to constipation in patients with cancer receiving palliative care is modest.[19] Our practice is to avoid high doses of oxycodone–naloxone to avoid dose-conversion dilemmas at later stages. At small doses, the dilemma is more academic than practical, and the product availability of low-dose oxycodone–naloxone (eg 2.5/1.25, 5/2.5 mg) when compared with, for example, modified release oxycodone (10 mg is the smallest dose) does make it appealing.

The Therapeutic Goods Administration recommends a maximum daily dose of 160/80 mg (ie 80/40 twice daily) per day.

Conclusion

This article reviewed common misunderstandings in palliative care, including that fentanyl products (patches and orally disintegrating tablets) are contraindicated in patients who are opioid-naïve and require careful consideration during rotation. Buprenorphine's partial agonist properties do not reduce the efficacy of other opioids for breakthrough pain, contrary to a common misconception. Equianalgesic tables, though helpful, have significant limitations derived from single-dose studies and fail to account for individual variability, making dose reduction critical during opioid rotation. Combined oxycodone–naloxone products offer modest benefits for constipation in patients with cancer receiving palliative care, but might fail in those with hepatic impairment or portal flow disruption. Healthcare practitioners should consider these factors and limitations when deciding on appropriate pain management strategies for patients with advanced cancer. Knowing the pitfalls and limitations in prescribing will help general practitioners avoid medication-related errors.

Authors

Taylan Gurgenci FRACGP, FAChPM, Palliative Care Specialist, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld; Clinician–Investigator, Mater Research Institute, University of Queensland, Brisbane, Qld

Jones Chen FRACGP, FAChPM, Palliative Care Specialist, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld

Benjamin Jull MPharm, FANZCAP (Generalist, MentalHlth), Acting Senior Mental Health Pharmacist, Pharmacy Department, Gold Coast Hospital and Health Service, Gold Coast, Qld

Claire Stokes FRACGP, Palliative Care Research Fellow, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld; General Practitioner, Camp Hill Medical Centre, Brisbane, Qld

Dominic Eu FRACP, Palliative Care Specialist, Department of Cancer Services, Mater Adult Hospital, South Brisbane, Qld

Phillip Good FRACP, PhD, Director of Cancer Services, Mater Adult Hospital, South Brisbane, Qld; Director, Palliative Care, St Vincent's Private Hospital, Brisbane, Qld; Professor, Faculty of Medicine, Mater Research Institute, University of Queensland, Brisbane, Qld

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Correspondence to:
t.gurgenci@uq.edu.au

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correspondence **ajgp@racgp.org.au**