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Madame/Sir

As a clinical pharmacologist, anaesthetist with intensive care training and pain medicine specialist with an academic positon at University of Western Australia and a clinical position in Pain Medicine at Royal Perth Hospital, I want to make the following submission on the Therapeutic Goods Administration Consultation Paper 'Prescription strong (Schedule 8) opioid use and misuse in Australia – options for a regulatory response'.

I will in the following address your options proposed in the order they are presented by you.

Option 1: Consider the pack sizes for Schedule 8 opioids

While theoretically any doctor can prescribe opioids in smaller amounts then the smallest package size and the opioids will then be dispensed in less than the smallest manufacturers' packaging size, it has become a dangerous habit by many to prescribe, for example, 20 oxycodone immediate-release as the standard discharge medication after day care or short stay surgery. This results in a potentially significant oversupply with the risk of continued use, overdose and diversion [1-3]. This is exemplified by a recent oxycodone overdose death in Perth, where a patient was discharged with a pack of 20 tablets ("as this is the normal size of the pack") and died of an overdose.

It would, therefore, be helpful to deliberately have manufacturers' packaging sizes in the order of 6 to 8, maximum 10 tablets to be targeted at one acute pain episode and discharge from hospital. This would set a clear signal that such small package sizes are preferable and would reduce the leakage of such medication into the community. The suggestion that the CMI for these packages in particular should include information about de-escalation and moving to non-opioid pain relief medication as well as to return unused medication to a pharmacy and not to share opioids with others would be useful in this context.

Option 2: Consider a review of the indications for strong opioids

This proposal is a difficult undertaking and would not, in general, influence prescribing of opioids greatly, as the information re the inefficacy of opioids in chronic non-malignant pain states is already well documented in many guidelines and policies [4-6]. However, it might be helpful to replicate such evidence-based statements in the PI of the opioids by, for example, clarifying indications as the treatment of chronic severe pain in malignancy, and then separately as the treatment of chronic pain of non-malignant causes and emphasise here the little evidence for

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long-term use, the limited efficacy to improve pain and even less to improve quality of life or function and outline the high risk of harm including deliberately mentioning tolerance and dependency development, opioid-induced hyperalgesia, opioid-induced androgen depression and immune depression as important issues which should be considered and monitored with long-term intake.

Option 3: Consider whether the highest dose products should remain on the market, or be restricted to specialist/authority prescribing

Again, here, a separation of pain due to malignancy from pain due to other causes would be important. However, it remains unclear whether the TGA has the option to actually introduce dose limits and specific rules for prescribing, and, therefore, it remains a question if the TGA is the right authority to introduce such changes. As already noted in the document by the TGA, the PBS would possibly be in a more suitable position to specify such limits or specialist-only authority prescribing, but as also outlined in the document that would not limit the use of private prescriptions, which are, in my understanding, already a specific problem with long-term use of opioids.

In principle, a 90 mg morphine-equivalent limit, as suggested by the CDC [7] and considered by the FDA, makes a lot of sense. One option which has been implemented in the S8 prescribing code of the state of Western Australia is that, for patients with no history of drug abuse, up to 90 mgs morphine equivalent can be prescribed by a GP without authority; exceeding this does requires authority by a specialist [8]. Such an approach gives the GP the leeway to use opioids in reasonable amounts but limits the prescription of high doses with increased risk of adverse effects including in particular fatal overdoses.

Option 4: Strengthening Risk Management plans for opioids products

Again, it is unclear to me if the TGA is in a position to mandate programs like REMS suggested by the FDA, which are in principle educational programs prescribers have to participate in before being permitted to prescribe opioids. Again, if this is an option the TGA has, then a more feasible option would be to introduce a dose limit below which such education is not required, possibly in the range of 90 mgs morphine equivalent, with a requirement to have attended a specifically designed program targeting the goals mentioned in the TGA document before being permitted to prescribe higher dose opioids.

The legislation which would permit this is for me difficult to imagine and possibly not practically feasible.

Option 5: Review of label warnings and revision to the Consumer Medicines Information

As already outlined under a previous point, I think it would be extremely important that the labelling is improved. I understand from the document that the TGA is already putting in to all prescription PIs the issue of returning unused medicine to the local pharmacy. Further changes beside the instructions on disposal, would have to aim at safe storage, keeping away from children in a more specific format, as well as

risks for driving, in particular subsequent to dose changes, and then a complete outline of the risk/benefit ratio for chronic pain management including highlights on the previously mentioned complications seen commonly with long-term use of opioids. The ones mentioned should at least include tolerance and dependency development, opioid-induced hyperalgesia, opioid-induced androgen depression and immune depression as important issues which should be considered and monitored with long-term intake. In addition, safe dose limits could be part of the PI.

Option 6: Consider incentive for expedited TGA review of improved products for pain relief and opioid antidotes

While abuse-deterrent opioids are potentially reducing the risks of inappropriate parenteral use of opioids, they are not, in principle, addressing the issue of long-term use of high-dose opioids in chronic pain. Data available to me based on observations in the United States are suggesting that abuse-deterrent preparations of opioids have only a limited effect on the overall usage of opioids and that people with addiction often and quickly find ways to circumvent the mechanism of abuse deterrence. However, there is no question that for full mu-agonists they are reducing the black-market value of opioid preparations and thereby the rate of diversion and as such these preparations should be supported.

In this context, it is of note that for OxyContin® there is now a branded abuse-deterrent preparation, but in contrast to the decision by the FDA, the TGA has nevertheless registered generic slow-release preparations of oxycodone in parallel, which are not an abuse deterrent. There is a clear indication from what I see among my patients, that patients are deliberately asking for the non-branded formulation, do not want to have "no generic substitution" on their scripts and are also bargaining with pharmacists about receiving the generic presentation with claims that the branded presentation is no longer as effective as in the past. Therefore, one simple and important step would be that, if there is an abuse-deterrent preparation available, all non-abuse-deterrent preparations should lose their registration.

With regard to a rapid and accelerated review of improved products for pain relief, there are currently not a lot of options on the horizon and while such an expedited review process would be helpful in case such substances have left the research pipeline, the impact on the overall abuse of opioids might be minimal.

In this context it might be more helpful that expedited reviews are not only done for new entities hitting the market, but also for new product information having to be inserted in the PI or CMI of already registered products as this process at the moment takes over a year; this might be disadvantaging products with an improved safety profile or endangering patients in the case of such information is not processed quickly.

Option 7: Potential changes to use of appendices in the Poisons Standard to provide additional regulatory controls for strong opioids

Such suggestions are clearly helpful and are partially already implemented in various states. For example, in Western Australia prescription by general practitioner,

beyond a threshold of a daily dose of 90 mgs morphine equivalent or with prescriptions containing to a large extent immediate-release preparations, require an authority by a specialist for ongoing prescribing [8]. The problem in Australia is that currently these restrictions are different from state to state and there is therefore a wide and different pattern of rules governing such prescribing. Standardising these rules through a federal agency would be an appropriate way of dealing with this problem. However, it is unclear to me how far legislation actually enables the TGA to take over the formulation of such rules from state governments.

Option 8: Increase health care professional awareness of alternatives to opioids in the management of chronic pain

This is clearly an important initiative and the attempts by NPS MedicineWise to initiate such approaches have to be applauded. It is highly recommended that the TGA cooperates with the Colleges involved and in particular the Faculty of Pain Medicine with regard to the development of educational material which could clearly become mandatory, although again it is unclear what legislation would be required to achieve this goal.

In this context, it is not only important to reiterate the sociopsychobiomedical nature of chronic pain {Carr, 2014 #23176} and its poor responsiveness to medical interventions, including medication use, and the much more important role of changing behaviour by approaches such as cognitive behavioural programs, education in self efficacy and self-management, promotion of physical activity and weight loss and psychological interventions such as mindfulness aiming for reduced fear-avoidance-behaviour, better sleep hygiene and improved coping strategies.

There is widespread evidence in the literature for the benefit of even short educational interventions to improve self-efficacy and self-management skills of patients [9] and also for the role of cognitive behavioural longer programs [10, 11]. However, these approaches are currently only of limited availability in the Australian healthcare landscape and often connected to long waiting times for multidisciplinary pain management centres [12].

In addition, for these measures to be successful requires a public education campaign on concepts of seeing chronic pain not as a curable disease, but as a chronic health condition which requires management, not cure. Such educational messages should also reduce the '*overmedicalisation*' of chronic pain states, the current focus on biomedical diagnosis and biomedical interventions and reformulate for example chronic musculoskeletal back pain not as a disease but as '*exercise intolerance*'. Such a public education campaign should target the general population via newspapers, magazines, TV productions and social media as well as for example pupils and students in the context of health education overall.

In this context it would also be highly important to promote a concept, which identifies relevant differences between opioids. From the available literature it is very clear that while most S8 drugs currently available are primarily relying on pure μ-agonism for their efficacy, there are 3 compounds, buprenorphine, tapentadol and tramadol, which differ from the other opioids. This difference has been highlighted for example

in the RACGP Guidelines for Prescribing of Opioids with regard to improved safety and possible different efficacy of these three compounds [6].

With regard to buprenorphine, there are large data sets which suggest that, in comparison to full μ-agonists, there are significant advantages with regard to reduced toxicity and reduced risk of respiratory depression [13]. This reduced risk is further assisted by the fact that the maximum permitted transdermal dose in Australia is currently 40 mcg per hour and such a low dose limit enhances the safety of the buprenorphine patch, for example, in striking difference to the fentanyl transdermal patch with much higher doses and a well-documented high risk of overdose and fatal outcomes [14]. Other advantages of buprenorphine which differentiate it from classical μ-agonists are a reduced risk of constipation, reduced risk of immune suppression, minimal induction of opioid-induced androgen deficiency, reduced risk of induction of tolerance and hyperalgesia, possibly a lower abuse potential and problems with withdrawal and established safety in elderly patients and patients with renal failure [15].

The other two medications, tapentadol in the S8 group and tramadol in the S4 group, are not classical -agonists and a major component of their analgesic effect does not result from agonism to the μ-receptor but from, in the case of tramadol, noradrenaline and serotonin reuptake inhibition and, in the case of tapentadol, from noradrenaline reuptake inhibition [16, 17]. They are therefore more correctly described as centrally acting atypical analgesics than as opioids.

Tramadol due to these properties has been regarded by chronic pain physicians as advantageous for many years [18, 19]. Other advantages are the lower abuse potential [20-22] and the reduced toxicity with regard to respiratory depression [23, 24].

These advantages are even more obvious in the case of tapentadol, which has none of the serotonergic properties that limit the usefulness of tramadol, in particular in combination therapy with many other agents due to the increased risk of serotonin syndrome [16]. Furthermore, tapentadol does not rely on cytochrome P450-2D6 metabolism for the μ-effect, but both properties, noradrenaline reuptake inhibition and μ-agonism, are in the parent molecule [25]. Its synergistic mechanism is again regarded by many pain medicine specialists as a significant advantage of tapentadol, in particular over conventional μ-opioid analgesics, again with regard to safety, but also with regard to efficacy.

With regard to safety, tapentadol overdoses are rarely fatal and, in a review ready for publication, we were only able to identify six fatal outcomes of overdose in now over 9 years of use in the USA and Europe and for a number of years less in Australia (publication in preparation). This is possibly also partially due to the effect of an upper dose limit of 500 mgs per day, which is different from conventional μ-agonists that currently have no recommended upper dose limit; this is actually an advantageous property, which limits the unacceptably high doses we see prescribed for pure μ-agonists (records I have personally witnessed are among others 480 mg methadone/day for pancreatitis causing torsades de pointes cardiac arrests treated

with an implanted defibrillator and over 1000mg/day oxycodone in multiple patients) . Tapentadol in comparison to full μ-agonists, in particular oxycodone, has also shown a much lower risk of abuse, drug-seeking behaviour, diversion and tolerance in a significant number of American studies [26-30]. This is confirmed by personal information from multiple drug abuse specialists in Australia, who report no relevant rate of tapentadol abuse or appearance on the black market.

In addition, tapentadol offers significant advantages with regard to not only pain relief, but more important quality of life and function, as shown in a number of studies in which oxycodone use in the same settings (chronic back pain and osteoarthritis), while improving pain scores, reduced quality of life and function [31]. This is in line with our experience in many patients we have rotated from pure mu agonists to tapentadol with excellent results with regard to benefits and reduced rates of adverse effects [32]. The particular benefits to mention are reduced nausea and vomiting and, importantly for long-term use, reduced constipation.

In the final comments your consultation document touches also on the possible role of Pharmaceutical Benefits Scheme Prescribing Controls. As outlined by you in the document, there are options to change prescribing behaviour through such measures, although one has to acknowledge that patients with drug-seeking behaviours are often prepared to go for private scripts, often issued by on-call or emergency GP clinics and, therefore, such a measure might not necessarily address some of the most concerning prescribing behaviours occurring currently.

I appreciate your consideration of this submission which is not completely referenced in the interest of space. In case of further interest more detailed evidence-based material can be provided by me.

Yours sincerely

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Conflict of Interest Declaration:

The Anaesthesiology Unit of the University of Western Australia, but not Professor Schug personally, has received research and travel funding and speaking and consulting honoraria from Andros Pharmaceuticals, Eli Lilly, bioCSL/Seqirus, Grunenthal, Janssen, Mundipharma, Pfizer, Phosphagenics, STADA, iXBiopharma and XGene Pharmaceuticals within the last 5 years.

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