

Navigating the evolving landscape in the prescribing of medications for insomnia in Singapore: Principles and considerations from a psychiatrist's perspective

Ho Teck Tan¹ MRCPsych, Chao Tian Tang¹ MRCPsych, Shian Ming Tan¹ MMED Psychiatry

ABSTRACT

There are significant challenges for medical practitioners who have to navigate complex clinical, legal, ethical and administrative considerations in the prescription of controlled medications in the treatment of insomnia. This commentary examines the changing landscape and reframing of risks associated with the use of benzodiazepines and Z-drugs in light of recent legal precedents based on Singapore's frameworks of the Singapore Medical Council's Ethical Code and Ethical Guidelines, and the Prescribing of Benzodiazepines Guidelines (MOH Clinical Practice Guidelines 2/2008). The recent ruling from the Court of Three Judges has shone a spotlight on rigorous justification in instances where there is deviation from established treatment guidelines and thorough risk-benefit analysis, particularly when considering off-label use of medications, which is not uncommon in the clinical setting. While the risks of long-term prescription of benzodiazepines should never be discounted, preservation of a patient's functioning and current quality of life should also be taken into consideration in the risk-benefit analysis. The complexities of transitioning patients from sedative hypnotics to alternative medications are also addressed, with an advocacy for licensed medications with established safety profiles.

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INTRODUCTION

The risks of prescribing benzodiazepines and Z-drugs for insomnia are well recognised by regulators, where the prescribing of such medications in contravention of guidelines has been the subject of regulatory action.^{1,2} Medical practitioners involved in the prescription of such medications need to grapple with complex clinical, legal, ethical and administrative considerations that may not be apparent at first glance. Consider, for example, a well-informed patient who has been visiting a

succession of doctors for insomnia where evidence of a substance use disorder is lacking. This patient has been prescribed with numerous benzodiazepines, including midazolam which he/she perceives to be the most efficacious. The patient may reference the National Drug Formulary (Singapore), and argue that midazolam, a short-acting but highly addictive benzodiazepine, is indicated in the short-term treatment of severe insomnia, and contend that the non-prescription of this medication is detrimental to his/her well-being. When presented with clinical practice guidelines for prescribing of benzodiazepines, one may quote the statement of intent of the guideline in that recommendations are not intended to serve as a standard of medical care and that every physician is ultimately responsible for an individualised approach with each patient.² Such a consultation is unlikely to end on a productive note, where practitioners now also need to take into consideration the recent legal developments that have been now enshrined in Singapore case law.³ In this commentary, we will discuss salient points with regard to these developments, and provide practical prescribing considerations in accordance with relevant principles.

Recent legal developments delivered by the Court of 3 Judges

The Court of 3 Judges, in the delivery of the judgment for Ang Yong Guan v Singapore Medical Council and another matter, set out that while the Singapore Ministry of Health (MOH) guidelines set forth a presumptive standard of care, departures from this may be permissible in individual cases. These instances should be justified or supported by good reasons. The same applies to the standards derived from the package inserts and product monographs of the different medicines prescribed. While this seems to favour the argument of the patient illustrated in the example, it was emphasised that the same burden falls upon the medical practitioner, with no distinction made

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¹ Department of Psychiatry, Sengkang General Hospital, Singapore

Correspondence: Dr Ho Teck Tan, Department of Psychiatry, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.

Email: tan.ho.teck@singhealth.com.sg

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between general practitioners or psychiatrists. There was also an emphasis in the judgement on treating the underlying condition that resulted in the patient's persistent use of benzodiazepines, instead of simply leaving it to any specialist to continue the prescription of benzodiazepines beyond the stipulated time limit of 8 weeks.

The judgment stressed that the psychiatrist does not have free reign to disregard the standards set out simply by virtue of being a specialist, and remains obliged to justify any departures from the presumed standards. Such justifications include considering why the guidelines exist and the relevant risks. Beyond considering the rationale behind that standard and conducting a risk-benefit analysis of each prospective departure, it would be essential as well to demonstrate that the psychiatrist had then come to an objectively defensible conclusion that the departure was justified under those circumstances.

Awareness of the current ethical framework for off-label drugs

Following clinical guidelines rather than deviating from them is a choice that most clinicians consider safe. However, there may be unrecognised pitfalls when generalising international guidelines to any local setting, given the need to also take into account local guidelines and regulations. Non-pharmacological methods (e.g. cognitive behavioral therapy for insomnia) are the first-line treatment options but here we limit our discussion to pharmacological options to highlight the challenges that clinicians can face when it comes to prescribing. In addition, many medications are used on an off-label basis in insomnia, and this may not be explicitly mentioned or discussed during patient consultations.⁴ In addition, the patients' consent to such use must be obtained if they are able to do so. However, the validity of such consent would be questioned if a patient was not informed that the medication was being used off-label. It is also important to note that off-label prescribing encompasses any modification of dosage regimen, administration route, pharmaceutical form, different indications, different age groups and different categories of patients beyond the licensing of these medications.⁵ To illustrate an example of what would be considered off-label prescribing in Singapore, some patients may prefer a lower dose of 2.5 mg of lemborexant (where there is evidence that this dose may sufficiently treat insomnia while minimising next morning residual sleepiness), instead of the licensed dose of 5–10 mg daily.⁶

While off-label prescribing may benefit different categories of patients, there are serious repercussions should due care not be carried out.⁵ The Singapore Medical Council's Ethical Code and Ethical Guidelines (SMC ECEG) requires medical practitioners, when using off-label drugs, to justify that it is in the patients' best interests.⁷ To elaborate, the SMC ECEG also mandates an assessment of the risks and benefits of such use, which is not endorsed by all jurisdictions around the world.⁸ In the treatment of insomnia, international guidelines include those by the American Academy of Sleep Medicine or the British Association for Psychopharmacology.^{4,9} However, these guidelines recommend benzodiazepines and Z-drugs, in contrast to Singapore guidelines. Medical practitioners may then be inclined to consider other medications mentioned in such guidelines, such as trazodone. However, not all medical practitioners may be well-equipped to counsel patients regarding off-label use of medications, as well as adequately document their provision of medical advice.¹⁰ In the Singapore setting of multidisciplinary and team-based care in restructured hospitals, good documentation and communication between different team members is important to maintain good continuity of care. Inadequate disclosure by a prior team member regarding off-label use of medication with subsequent revelation by other team members may lead to negative patient experience, a rupture in the therapeutic alliance and medico-legal issues, particularly if adverse effects from such use emerge.

Going back to basics: Start first with licensed medications with clinical evidence for safety and value!

Currently, there are efforts internationally to contain spiralling healthcare costs via standardisation. Factors such as variations in clinical practice with a lack of standardisation has been shown to increase cost unnecessarily and impact the quality of care.¹¹ While off-label prescribing is not uncommon in the treatment of insomnia, the lack of strong evidence for this practice adds to significant variation in clinical care with subsequent implications for safety and costs.⁴ One potential contributor to this variation is the perception of the concept of off-label prescribing among patients. In a study to understand public perceptions of approved versus off-label use for COVID-19-related medications via an analysis of 609,189 tweets on social media,¹² the authors found varied perceptions and stances on off-label versus U.S. Food and Drug Administration-authorized drug use across different stages of

COVID-19.¹² These variations, in addition to the legal and ethical need to discuss off-label prescribing vis-à-vis the aforementioned court judgment, will invariably impact consultation times and therefore costs as well.

One potential solution is to prioritise licensed medications for insomnia in care pathways for the management of insomnia. To our knowledge, the only 2 medications in Singapore currently licensed for the treatment of insomnia are lemborexant and melatonin (prolonged release), which been shown to be efficacious and safe.^{13,14} These medications lack the clinical, ethical and legal risks associated with addictive medications like benzodiazepines or Z-drugs. Lemborexant, an orexin receptor antagonist, is indicated for the treatment of adult patients with insomnia- characterised by difficulties with sleep onset and/or sleep maintenance—with no restrictions on duration of use.¹⁵ Melatonin (prolonged release) is indicated for short-term treatment of primary insomnia in patients who are aged 55 or over.¹⁶ As both are currently not subsidised by MOH, further cost-effectiveness studies may justify their inclusion in the Standard Drug List.^{15,16}

For patients already on benzodiazepines and Z-drugs, medical providers need to exercise caution with regards to their continued prescription beyond 8 weeks. This may involve a thorough assessment regarding the underlying factors that resulted in the patient's continued use of benzodiazepines.³ When prescribing of benzodiazepines and other hypnotics, it would be prudent for medical practitioners to begin with an endpoint in mind as the Administrative Guidelines issued by MOH in 2008 suggested that patients who were already on high-dose and/or long-term benzodiazepines initiated by their specialists should be referred back to these specialists for further management.¹⁷

Medical providers could consider facilitating patients' transition from sedative-hypnotics to other medications. A recent 2024 study has reported a significant number of successful transitions from Z-drugs and other hypnotics to lemborexant with no serious treatment-emergent adverse events, bearing in mind however that this was an open-label multicentre study involving 90 patients.¹⁸ Studies have also looked at melatonin in a similar manner.¹⁹ If patients still need to be continued on benzodiazepines or Z-drugs for a duration beyond that endorsed in existing guidelines, medical practitioners should endeavour a nuanced risk-benefit analysis, taking into consideration the preservation of a patient's functioning and current quality of life against potential side effects. Ultimately, clinicians need to balance many

requirements including clinical and legal obligations with the need to provide patient-centred care for the best possible outcomes. In so doing, value-based outcomes are improved, and truly more care is achieved.

Declaration

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