



Evidence behind red pop-up notifications and alerts

Introduction

SafeScript NSW contains clinical alerts which are displayed where a high-risk situation has been detected in a patient's prescription or dispensing record for monitored medicines. The alerts are generated in real time, as the events are recorded in the system. Alerts are red or amber, depending on the potential for harm. This fact sheet contains information about how each of the alerts works, and the clinical evidence that supports each alert.

Clinical decision making remains with the health practitioner

It is critical to note that the alert in SafeScript NSW does not instruct clinicians on what to do or whether a medicine should or should not be provided. This decision remains with the clinicians involved in the care of the patient. SafeScript NSW provides additional information and context to help inform this decision.

The clinicians involved in the care of the patient remain best placed to consult with the patient and determine whether these medicines remain the safest and best option based on the individual's health needs and circumstances.



1. Concurrent prescribing of potentially harmful medicines alerts

1.1 Why are concurrent prescribing of potentially harmful medicines alerts included in SafeScript NSW?

- Serious toxicity and overdose are associated with co-prescribed opioids with benzodiazepines, antidepressants and antipsychotics.¹
- Patients with overlapping concurrent prescriptions for opioids and benzodiazepines have a more than nine-fold higher risk of overdose compared with matched controls receiving opioids or benzodiazepines alone or neither.²
- Benzodiazepines are associated with opioid overdose in patients taking prescription opioids long-term.³
- There is a substantial increase in relative risk of unintentional overdose for patients receiving concomitant opioid and z-drugs treatment.⁴
- Fentanyl, methadone and morphine possess the highest relative fatal toxicity within the class of Schedule 8 opioid drugs.⁵
- Benzodiazepines have been identified as the second most common class of drug involved in unintentional drug-induced deaths, usually in polysubstance overdose deaths, in Australia.⁶
- Compared with patients exposed to opioids alone, patients exposed to opioids, benzodiazepines, and non-benzodiazepine sedative-hypnotics in combination, are approximately 60% more likely to overdose.⁷
- The risk of overdose from fentanyl amongst people who inject the drug is approximately eight times that of the injecting of other prescribed Schedule 8 opioid drugs.⁸

1.2 What will trigger these alerts?

This alert is triggered when prescribing and/or dispensing events for certain opioid and benzodiazepine receptor agonist (benzodiazepines, zolpidem, zopiclone) combinations are identified within the last 30 days.

The opioid and benzodiazepines receptor agonists included in this alert are:

- Long acting fentanyl products
- Methadone products that are generally prescribed for management of chronic pain*
- Benzodiazepine receptor agonists (all benzodiazepines as well as zolpidem/zopiclone)

A red notification will appear for prescribing and dispensing events for patients in this situation. Checking the corresponding alert in SafeScript NSW is then required to progress.

**Methadone products that are commonly prescribed as opioid substitution therapy as part of the NSW Opioid Treatment Program are not included in this alert category.*



2. Opioid dose threshold alerts

2.1 Why is an opioid dose threshold alert included in SafeScript NSW?

- Opioids have been identified as the primary class of drug involved in unintentional drug-induced deaths in Australia.⁶
- Life threatening opioid related respiratory, or CNS depression and overdose are strongly associated with mean daily prescribed morphine equivalent doses of 100mg or greater.¹
- Overdose mortality is associated with mean daily morphine milligram equivalents of greater than 100mg.¹⁰
- Daily opioid doses of 100mg oral morphine equivalent daily dose or greater are associated with a risk of unintentional overdose more than 5 times that of doses below 20mg oral morphine equivalent daily.¹¹

2.2 What will trigger an opioid dose threshold alert?

This alert rule will trigger for prescribing and dispensing events for patients whose average total daily opioid dose is currently 100mg morphine equivalent or greater for any dispensed monitored medicines. The alert is generated based on a rolling average over the previous 90 days.

A red notification will appear in this situation. Checking the corresponding alert in SafeScript NSW is then required to progress.

The average 90-day morphine equivalent dose (MED) is determined by calculating the MED associated with each transaction (Transaction MED) and adding these together to form a cumulative total for all dispense events in the last 90 days.

The Transaction MED value is determined using the following formula:

$$\frac{\text{Medicine Strength} \times \text{MED conversion factor} \times \text{Dispense Qty}}{90 \text{ days}} = \text{Dispense Transaction MED}$$

When a new transaction enters the database, its transaction MED value is added to the rolling 90-day total. If this addition means that the rolling 90-day total reaches or exceeds 100mg, a red alert is generated.

The morphine equivalent dose calculated by the SafeScript NSW system is not the same as an Oral Morphine Equivalent Daily Dose (OMEDD). An OMEDD is calculated based on the prescribed dose, whereas the morphine equivalent dose calculated by SafeScript NSW is based on an average of the medicines supplied to the patient.

Care needs to be taken with calculating the oral morphine equivalence. There is often variability in conversion factors and the patient may not be taking all the opioid medication being dispensed to them. An [Opioid calculator](#) has been developed by the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists (FPM ANZCA) to assist practitioners in conducting these calculations. The conversion factors used by SafeScript NSW align to the FPM Calculator, with the exception of Methadone, which uses a conversion factor of 3.



3. Multiple provider episode alerts

3.1 Why are multiple provider episode alerts included in SafeScript NSW?

- Overdose risk increases with concurrent prescriptions for opioids and benzodiazepines. The risk increases with concurrent prescribing by multiple prescribers.⁹
- There is an increased risk of opioid-related overdose death associated with four or more prescribers or four or more dispensing pharmacies.¹⁰

3.2 What will trigger multiple provider episode alerts?

A multiple provider alert will be triggered when the patient is receiving monitored medicines from multiple prescribers from different clinics. It is common for patients to see more than one prescriber at the same clinic. For this reason, prescribe events from prescribers in the same clinic are only counted as a single prescriber when this alert is calculated.

A red alert will trigger when prescribing events for monitored medicines from four or more prescribers from different medical practices in the last 90 days are identified in a patient's SafeScript NSW record.

An amber alert will be triggered when a patient has had prescriptions for monitored medicines dispensed at four or more pharmacies in the past 90 days. While there are many circumstances where this may be considered appropriate, health practitioners should be aware this behaviour, when associated with the use of monitored medicines, can be linked to oversupply of medicines and an increased risk of harm.¹⁰

4. Patient enrolled in the Opioid Treatment Program (OTP) alerts

4.1 Why are patients enrolled in OTP alerts included in SafeScript NSW?

- Patients undergoing treatment with OTP have an increased risk of overdose and opioid toxicity when used in combination with Central Nervous System (CNS) depressants.^{12,13}
- Combined use of OTP medicines with CNS depressants drugs increases risk of overdose, respiratory depression and death.^{14,15}

4.2 What will trigger patient enrolled in OTP alerts?

This alert rule will trigger for prescribing events where the medicine is a CNS depressant or sedating medicine, if the patient is currently enrolled in the Opioid Treatment Program (OTP).

An amber alert is triggered if the prescriber is the approval holder or authorised under the approval*.

A red alert is triggered if the prescriber is not the approval-holder, nor authorised under the approval*.



5. Medicine requires approval alerts

5.1 Why are medicine requires approval alerts included in SafeScript NSW?

- Some medicines e.g. dexamfetamine require approval prior to prescribing.
- Another prescriber has a current approval for the patient. Multiple prescribers can result in duplication of treatment and increased risk of harm.

5.2 What will trigger medicine requires approval alerts?

A Medicine Requires Approval alert informs the prescriber either that they require an approval for the medicine being prescribed; or that another prescriber already holds an approval for this patient for the category of medicine being prescribed.

This alert rule will trigger in the following scenarios:

- A red alert is triggered if one or more other prescribers hold a current approval for this patient for the category of medicine being prescribed, and the prescriber is not authorised under the approval*.
- An amber alert is triggered if the medicine being prescribed is a Schedule 8 psychostimulant, no prescribers hold a current S8 Psychostimulants approval for this patient, and the prescriber does *not* have one of the following specialties:
 - Specialist psychiatrist,
 - Specialist neurologist,
 - Specialist paediatric neurologist,
 - Specialist paediatrician,
 - Specialist general paediatrician
 - Specialist respiratory and sleep medicine physician
 - Specialist paediatric respiratory and sleep medicine physician

* *Authorised under the approval:*

The approval holder *or* the medical practitioner or nurse practitioner is practising at the same premises that the holder of the authority was practising at when the approval was issued



References

1. Zedler B, Xie L, Wang L, Joyce A, Vick C, Kariburyo F, Rajan P, Baser O, Murrelle L. (2014). Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. *Pain Medicine*; 15: 1911-1929.
2. Alobaidi A, Pickard AS, Jarrett JB, Lee TA. (2021). Hospitalizations for opioid-related overdose and timing of concurrent opioid and benzodiazepine use: A nested case-control study. *Pharmacotherapy*; 41: 722-732.
3. Khan N, Bykov K, Glynn RJ, Barnett ML, and Gagne JJ. (2021). Coprescription of Opioids With Other Medications and Risk of Opioid Overdose. *Clinical Pharmacology and Therapeutics*; 110 (4). 1011-1017.
4. Szmulewicz A, Bateman BT, Levin R, Huybrechts KF. (2021). The Risk of Overdose With Concomitant Use of Z-Drugs and Prescription Opioids: A Population-Based Cohort Study. *American Journal of Psychiatry*; 178 (7). 643–650; doi: 10.1176/appi.ajp.2020.20071038
5. Brett J, Wylie CE, Raubenheimer J, Isbister GK, Buckley NA (2019). The relative lethal toxicity of pharmaceutical and illicit substances: A 16-year study of the Greater Newcastle Hunter Area, Australia. *British Journal of Clinical Pharmacology*; 85: 2098-2107.
6. Penington Institute. (2021). *Australia's Annual Overdose Report 2021*. Melbourne: Penington Institute.
7. Cho J, Spence MM, Niu F, Hui RL, Gray P, Steinberg S. (2020). Risk of Overdose with Exposure to Prescription Opioids, Benzodiazepines, and Non-benzodiazepine Sedative-Hypnotics in Adults: a Retrospective Cohort Study. *Journal of General Internal Medicine*; 35 (3): 696-703.
8. Latimer J, Ling S, Flaherty I, Jauncey M, Salmon AM. (2016) Risk of fentanyl overdose among clients of the Sydney Medically Supervised Injecting Centre. *International Journal of Drug Policy*; 37: 111-114.
9. Chua K-P, Brummett CM, Ng S, Bohnert ASB. (2021). Association Between Receipt of Overlapping Opioid and Benzodiazepine Prescriptions From Multiple Prescribers and Overdose Risk. *JAMA Network Open*; 4 (8). Available at *JAMA Network Open*. 2021;4(8):e2120353. doi:10.1001/jamanetworkopen.2021.20353 Accessed October 28,2021.
10. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. (2014). High-Risk Use by Patients Prescribed Opioids for Pain and Its Role in Overdose Deaths. *JAMA Intern Med*; 174 (5) 796-801. doi:10.1001/jamainternmed.2013.12711. Published online March 3, 2014.
11. Adewumi AD, Hollingworth SA, Maravilla JC, Connor JP, Alati R. (2018) Prescribed Dose of Opioids and Overdose: A Systematic Review and Meta-Analysis of Unintentional Prescription Opioid Overdose. *CNS Drugs*; 32: 101-116.
12. Weschules DJ, Bain KT, Richeimer S. Actual and potential drug interactions associated with methadone. *Pain Med*. 2008;9(3):315–44. DOI: 10.1111/j.1526-4637.2006.00289.x PubMed PMID: 18386306. [PubMed] [Google Scholar]
13. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict*. 2010;19(1):4–16. DOI: 10.1111/j.1521-0391.2009.00005.x PubMed PMID: 20132117 PubMed Central PMCID: PMC3334287. [PMC free article] [PubMed] [Google Scholar]
14. Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Settings. Geneva: World Health Organization; 2009. 6, Methadone maintenance treatment. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK310658/>
15. Kumar R, Viswanath O, Saadabadi A. Buprenorphine. [Updated 2023 Nov 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459126/>