Royal College of Emergency Medicine

Best Practice Guideline

NPIS

Royal College of Emergency Medicine and National Poisons Information Service

Guideline for the Assessment and Management of Acute Opioid Toxicity in Adults in the Emergency Department

Last revised
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Summary of Recommendations

1) In acute opioid toxicity, the aim of naloxone administration should be reversal of respiratory depression and maintenance of airway protective reflexes, not full reversal of unconsciousness.

2) Adverse effects from naloxone are more likely to occur when excessive doses of naloxone are used.

3) Generally, patients should be observed for at least four hours after the last dose of naloxone and for at least six hours after the suspected time of opioid use. The length of the observation period may need to be adjusted from this standard depending on the duration of the effect of the opioid(s) taken.

4) The treatment of patients who have experienced a non-fatal overdose provides a valuable opportunity to provide brief intervention, onward referral to drug liaison services, and to promote engagement with community services.

Contents

Scope

The scope of this guideline is limited to the initial management, in the Emergency Department, of acute opioid toxicity related to the use of illicit opioids, and/or misuse (non-medical use), or deliberate self-poisoning (overdose) of prescription and over the counter opioids. It is not applicable for opioid toxicity in patients taking prescribed opioids for palliative care/cancer pain (follow guidance on TOXBASE for management of these patients), or for managing acute opioid toxicity in settings other than Emergency Departments.

Introduction

Acute opioid toxicity is a common reason for presentation to Emergency Departments in the UK and constitutes a significant burden on emergency health services. Presentations are more common at weekends, in the late evening and at night, but can occur at any time of the day[1].

Across Europe, opioids are the drugs most frequently encountered in acute drug toxicity presentations to the Emergency Department (heroin in particular, but presentations involving other opioids, including methadone, are also common)[1,2]. In relation to other Class A drugs 1,085,000 16 to 59-year-olds in England and Wales reported use of any class A drug in the last year; 64,000 of these were opioids including heroin or methadone[3].

Acute opioid toxicity has a high potential for significant mortality. Opioid related drug deaths are common, averaging 60 per week in Great Britain in 2022[4-6]. In Scotland the rate of drug poisoning deaths was 2.7 times as high as the UK average in 2022 and opiates/opioids were implicated in 82% of all drug misuse deaths[7]. Increasing trends in mortality related to prescription opioid misuse have also been noted since 2013 across Europe[8].

There have been an increasing number of new psychoactive substances (NPS) reported in Europe in recent years. Since 2009, a total of 74 NPS opioids have been identified on the European drug market; these are often found in products purported to be heroin and so users may not be aware that they are using these novel opioids[9]. These synthetic NPS opioids are often highly potent and/or longer acting than heroin, meaning that a typical street dose can pose an increased risk of life-threatening acute opioid toxicity, particularly as users may not be aware that they are being exposed to a novel opioid when using drugs such as heroin[9].

There have been several outbreaks of severe acute opioid toxicity and deaths relating to novel opioids such as fentanyls and nitazenes (e.g. isotonitazene which has twice the potency of fentanyl) in recent years[10]. These have led to spikes in drug-related deaths in England in 2017, 2021 and 2023[11], prompting local and national concern and making the management of opioid toxicity in the Emergency Department even more relevant today.

Identification of opioid toxicity

Acute opioid toxicity typically causes the triad of i) drowsiness (CNS depression); ii) respiratory depression (hypoventilation and reduced respiratory rate); and iii) pupillary miosis.

Other symptoms and signs may be present and can include[12]:

- Nausea and vomiting
- Neuropsychiatric features including nightmares, anxiety, agitation, euphoria, dysphoria, depression, paranoia and hallucinations
- Urticaria and pruritis

- Convulsions
- Hypotension and bradycardia
- Hypothermia secondary to environmental exposure

Commonly, opioids are co-ingested with alcohol or other drugs that can exacerbate respiratory depression (benzodiazepines and GABA-ergics such as pregabalin)[13], or with other drugs that result in mixed toxicity (sympathomimetics such as crack cocaine, or synthetic cannabinoid receptor agonists)[1] which may mask the typical opioid toxidrome and/or result in additional adverse effects.

The severity and duration of opioid toxicity will vary depending on the amount of opioid used, the potency of the opioid(s), the opioid tolerance of the individual and the route of use (oral, inhalation and/or intravenous).

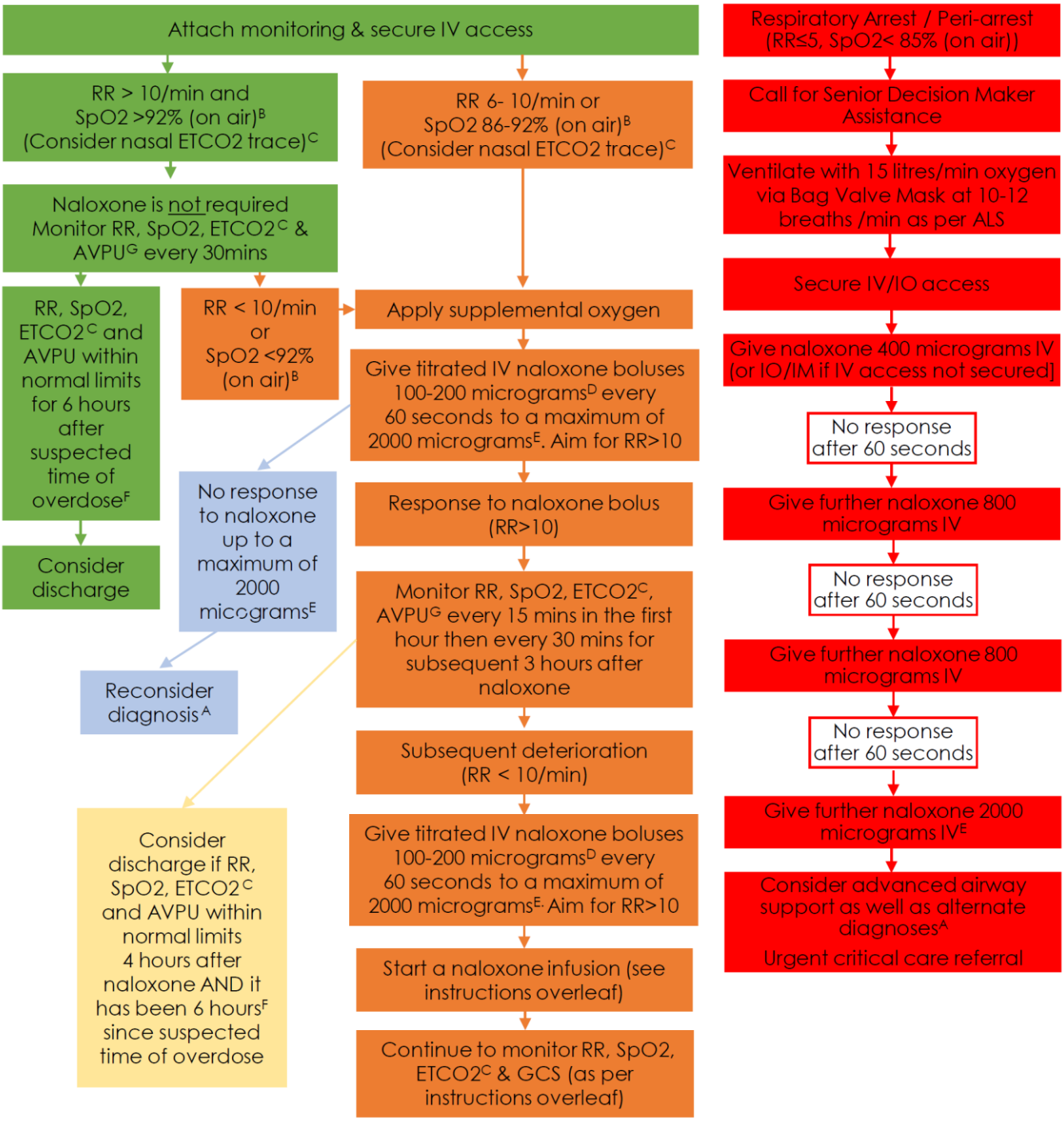
Urine drug screening has no role in the immediate clinical management of patients presenting to the emergency department where acute opioid toxicity is clinically considered. The diagnosis of an opioid toxidrome is clinical and should be based on history, symptoms, and signs. Naloxone can be a useful diagnostic agent in a patient with drowsiness and significant respiratory depression. In cases where there is uncertainty regarding the presentation discussion with a clinical toxicologist via the National Poisons Information Service (NPIS) is recommended.

Management

Naloxone is widely accepted as the antidote for opioid toxicity. It acts as a mu-opioid receptor antagonist. Naloxone can have a role not only to treat opioid toxicity, but also as a therapeutic trial in those respiratory depression and suspected opioid toxicity. The preferred route of use for naloxone in the Emergency Department is intravenous, but it can also be administered intramuscularly (IM), intranasally (IN)[14] or intraosseously (IO) – these routes should generally *only* be considered in the emergency department for patients in whom intravenous access is difficult or not possible. It should be noted that the IM and IN routes of administration are associated with a longer time to peak blood concentrations of naloxone. We actively discourage giving IM naloxone alongside IV naloxone, or IM naloxone prior to discharge of patients with acute opioid toxicity.

Figure 1: Management of suspected acute opioid toxicity in adults in the ED[A]

(this should NOT be used for opioid toxicity in patients taking prescribed opioids for cancer pain)



A. Always consider alternate diagnoses, investigations should include BM, VBG, paracetamol concentration ± CT Head
B. Interpret saturations with caution in those with pre-existing respiratory disease such as COPD
C. If available (and clinicians are experienced in its use), nasal ETCO2 can be used as an adjunct to the clinical assessment of ventilatory status to aid decision making, but it should be interpreted with caution in those with pre-existing respiratory disease and in context of the history and clinical signs
D. Initial naloxone bolus doses should be 100 micrograms, if the patient does not respond to four 100 microgram boluses, subsequent bolus doses should be 200 micrograms. Draw up 1x 400 microgram naloxone vial in a 10mL syringe and make up to 10mL with saline. A 100 microgram bolus will be 2.5mL and a 200 microgram bolus will be 5mL.
E. Those with severe toxicity or exposed to highly potent opioids may require larger doses of naloxone (more than 4 mg)
F. If a patient reports, or the clinician suspects, use of a longer acting opioid such as methadone or an NPS opioid the observation period should be extended up to 12 hours.
G. Whilst it is useful to monitor level of consciousness (AVPU, GCS), the aim of naloxone administration should be reversal of respiratory depression and maintenance of airway protective reflexes, not full reversal of unconsciousness.

This is a suggested pathway for management and not a mandatory standard of care. Clinicians (particularly senior decision-makers with sufficient anaesthetic training) may choose use alternative approaches, including oxygenation with permissive hypercapnia, or lower bolus doses of naloxone, and tolerate lower respiratory rates than suggested here.

It is important to note that the recommended dosing of naloxone depends on the circumstances of exposure and severity of respiratory depression. In the hospital setting, smaller intravenous doses are preferable for initial (non-respiratory arrest) treatment as this enables the clinician to ascertain the dose required to reverse respiratory depression whilst also avoiding the risk of acute iatrogenic opioid withdrawal[15]. This is key as although opioid reversal leading to acute iatrogenic opioid withdrawal is not typically life-threatening it may be compounded by overzealous opioid reversal unmasking stimulant toxicity in individuals who have used opioids with stimulants such as cocaine or methamphetamine. Measures to control an agitated patient in this situation, such as chemical or physical restraint or paralysis and intubation, may have negative consequences and carry significant risk for both patients and staff[16]. The process of acute opioid withdrawal is often distressing to patients and may cause patients to avoid accessing healthcare[17]. The importance of avoiding acute opioid withdrawal to reduce negative patient experiences and provide an opportunity for secondary prevention in a calm setting cannot be overstated.

Table 1: Features of acute opioid withdrawal.

Features of acute opioid withdrawal	
Yawning	Coughing
Sneezing	Running nose
Lacrimation	Hypertension
Tachycardia	Dilated pupils
Diarrhoea	Cool, clammy skin
Fine muscle tremor	Nausea
Irritability	Restlessness
Anxiety	

In acute opioid toxicity, the aim of naloxone administration should be reversal of respiratory depression and maintenance of airway protective reflexes, not full reversal of unconsciousness. Although level of consciousness (e.g. AVPU, GCS) can be useful to monitor, therapeutic targets should be a respiratory rate of over 10 breaths per minute and oxygen saturations of greater than 92% on room air (in the absence of pre-existing respiratory disease such as COPD where target saturations may routinely be 88-92%). Additionally, if available and where clinicians are experienced with its use, nasal end-tidal carbon dioxide monitoring can be used as an adjunct to the clinical assessment of ventilatory status to aid decision making.

Naloxone is generally well tolerated, but reported adverse effects of naloxone include nausea, vomiting, sweating, tachycardia, tremor, hyperventilation, and hypertension; these effects are more likely to occur when excessive doses of naloxone are used, reinforcing the importance of using titrated doses of naloxone to avoid inducing acute opioid withdrawal related to opioid reversal[18,19]. Less commonly cardiac adverse effects may occur, particularly in patients who are taking opioids for pain relief and have pre-existing cardiac disease: hypo-or hypertension, pulmonary oedema, atrial and ventricular fibrillation, and cardiac arrest have been reported. However, these adverse effects may have resulted from non-cardiogenic pulmonary oedema related to the opioid rather than an unwanted effect of the naloxone. Finally, there are rare reports of convulsions following the use of

naloxone; however, a causal link has not been shown and there is the potential that these convulsions may have been related to drugs co-used with opioids rather than to naloxone[20]. Clinically it is difficult to ascertain whether many of the reported adverse effects of naloxone relate to co-used drugs or the opioid toxicity itself.

Commencing a Naloxone infusion

As noted in Figure 1, incremental IV boluses of Naloxone (100-200 micrograms every 60 seconds) should be administered until the respiratory rate is greater than 10 breaths per minute. Patients may require large doses of up to 2-4 mg, but it is important that naloxone is given in small incremental doses to decrease the risk of acute withdrawal syndrome related to opioid reversal. Following an initial response, if the patient subsequently deteriorates and requires further IV boluses of naloxone to maintain adequate ventilation, they will require a naloxone infusion.

It is recommended to start with an hourly infusion rate of naloxone of 60% of the total dose(s) of naloxone that were required to adequately reverse the respiratory depression during the second dosing of naloxone.

With high dose infusions, be aware that the syringe may need replacing relatively soon, and it may be appropriate to provide a follow-on prescription at the same time as the initial prescription.

Preparation: Mix 4 mg (10 x 400microgram/1mL vials) of Naloxone with 30 mL of 0.9% sodium chloride solution (dextrose can be used as an alternative), to provide a final 40mL volume with a concentration of 100 microgram/mL, for infusion using an IV pump.

Administration: Table 2 gives indicative starting infusion rates in microgram/h and mL/h of prepared solution.

Table 2: Recommended starting infusion rates for naloxone infusions

Total initial bolus dose required for response	Starting infusion rate (microgram/h)	Starting infusion rate (mL/h)
200 micrograms	120 microgram/h	1.2 mL/h
400 micrograms	240 microgram/h	2.4 mL/h
600 micrograms	360 microgram/h	3.6 mL/h
800 micrograms	480 microgram/h	4.8 mL/h
1000 micrograms	600 microgram/h	6.0 mL/h
1200 micrograms	720 microgram/h	7.2 mL/h
1400 micrograms	840 microgram/h	8.4 mL/h
1600 micrograms	960 microgram/h	9.6 mL/h
1800 micrograms	1080 microgram/h	10.8 mL/h
2000 micrograms	1200 microgram/h	12.0 mL/h

Monitoring of patients on a Naloxone Infusion

Once commenced the naloxone infusion should be titrated to the desired clinical effect. Patients on naloxone infusions require frequent observation, initially every 15 minutes for the first hour after the infusion is started and then every 30 minutes. If a patient on a naloxone infusion shows signs of respiratory depression (respiratory rate of less than 10 breaths per minute, oxygen saturations on room air of less than 92% and/or a concerning end tidal carbon dioxide trace), further IV boluses of 100-200 micrograms naloxone should be given every 60 seconds up to a maximum of 2mg to achieve a respiratory rate of over 10 breaths per minute. The infusion rate per hour can then be increased by 60% of the total bolus dose of naloxone that was required. If a patient on a naloxone infusion begins to show signs of acute opioid withdrawal syndrome the infusion rate should be decreased, generally by 50% in the first instance, but if the patient is significantly agitated the naloxone infusion can be stopped temporarily; the infusion can be restarted after 30-60 minutes, at 50% of the previous infusion rate per hour once the withdrawal settles. If the naloxone infusion dose/rate is changed, more frequent monitoring should recommence with observations every 15 minutes for the first hour and every 30 minutes thereafter.

Stopping a Naloxone Infusion

After commencing a naloxone infusion, unless there is evidence of recurrence of toxicity or acute withdrawal, the infusion should continue at the same rate for at least four hours before starting to titrate the infusion down. It should then be down titrated by 25% of the maximum infusion rate every two hours whilst the patient continues to undergo close observation for signs of recurrence of toxicity or acute withdrawal.

It is unlikely that the titration of a naloxone infusion down will be done within the ED unless there are significant delays in organising admission.

A naloxone infusion should not generally be stopped at night (midnight to 0600) unless the patient is experiencing features of acute opioid withdrawal syndrome because recurrence of acute toxicity may be more difficult to routinely detect overnight if the patient is sleeping.

Discharge following the use of Naloxone

Patients treated with naloxone and responding with normal observations and mental state may be discharged after an appropriate observation period. Ideally, patients should be observed for at least four hours after the last dose of naloxone and for at least six hours after the suspected time of opioid use. **However,** the length of the observation period may need to be adjusted from this standard depending on the duration of the effect of the opioid(s) taken. If a patient reports using a longer acting opioid or the clinician suspects this (e.g. methadone or an NPS opioid), the observation period may need to be extended up to 12 hours.

Secondary prevention

One longitudinal study in the US found that at 12 months following a non-fatal opioid overdose, patients died at approximately 24 times the rate of the general population[21]. Causes of death included drug use-associated diseases, HIV, chronic respiratory diseases, viral hepatitis, and suicide.

During a presentation to the emergency department secondary to acute opioid intoxication and/ or overdose, emergency clinicians should always consider the opportunities for brief intervention, onward referral to drug liaison services, and encourage engagement with existing community services.

Brief intervention can be provided in the form of verbal or written advice (see Appendix 1: Messages for people who use drugs). Clinicians should be aware of the local drug liaison services in their area and encourage engagement with routes to opiate substitution therapy.

Provision of take-home naloxone varies depending on local commissioning arrangements, but increasingly both in-hospital and community drug services can provide take home intramuscular or nasal naloxone products[22], and provide the associated training to administer them. This is an intervention known to reduce drug related deaths[23,24].

Finally, presentations with acute opioid toxicity should be used as opportunities to consider blood borne virus testing in this high-risk cohort as well as homelessness referral if applicable. Emergency departments in England have a legal duty to refer someone who they believe to be experiencing homelessness, or to be threatened with becoming homeless within 56 days, to a local housing authority of their choice[25].

About this Document

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NPIS Clinical Standards Group

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Endorsements

None.

Review

Usually within three years or sooner if important information becomes available.

Declaration of Interests

DMW: Is a member of the UK Advisory Council on the Misuse of Drugs and an expert advisor to the European Monitoring Centre for Drugs and Drug Addiction and the United Nations Office on Drugs and Crime. He is also a Clinical co-ordinator at the UK National Confidential Enquiry into Patient Outcomes and Death, and on the Editorial Board of the Journal of Medical Toxicology. His work on these guidelines was independent of his roles with these organisations.

CH: Is an editor for the Emergency Medicine Journal, has received payments from Elsevier for educational articles, has been re-imbursed for travel expenses by RCEM, and is a recipient of grants from the Centre for Precision Cell Therapy for the Liver. His work on these guidelines was in his role as a member of the RCEM Toxicology Special Interest Group.

PID: Is an adviser to the UK Advisory Council on the Misuse of Drugs, the European Monitoring Centre for Drugs and Drug Addiction the United Nations Office on Drugs and Crime, and the World Health Organisation. He is also a Commissioner to the UK Commission Human Medicines, on the Senior Editorial Board of Clinical Toxicology, and is the President Elect of the European Association of Poisons Control Centres and Clinical Toxicologists. His work on these guidelines was independent of his roles with these organisations.

No other declarations.

Disclaimers

The College recognises that patients, their situations, Emergency Departments and staff all vary. This guideline cannot cover all possible scenarios. The ultimate responsibility for the interpretation and application of this guideline, the use of current information and a patient's overall care and wellbeing resides with the treating clinician.

Research Recommendations

Research to establish safe and acceptable criteria for discharge after naloxone administration would be beneficial.

Research to establish the role of emergency care providers in secondary prevention following non-fatal overdose in a UK setting would be beneficial.

Audit Standards

Adherence with these guidelines.

Key words for search

Best Practice Guideline, Acute Opioid Toxicity.

Appendix 1 - Messages for people who use drugs

***Adapted from: 'Guidance for local areas on planning to deal with potent synthetic opioids*[*]**

Drug supplies change, best test first

What's in your drugs can change frequently and your dealer doesn't always know what's in them or how powerful they may be. It is best to start with a small amount or inject slowly to test the effect.

Look out for your mates

If possible, use with your mates. Using alone is much more risky as there is no one to look out for you if you overdose.

Look out for the signs of overdose

An overdose won't always look the same but some of the signs to look out for are:

Falling unconscious

Very light shallow breathing or no breathing

Loud raspy 'snoring' or gurgling

Blue or pale lips or fingertips

Call an ambulance

If someone overdoses call 999 immediately and ask for an ambulance.

Naloxone: get it, carry it, use it

The main messages for giving someone naloxone are:

If someone overdoses: act fast, don't wait to see if they will recover – you could save their life

Remember, call an ambulance immediately

Check the person is breathing

Put them in the recovery position: on their side with their head resting on their arm

Give them naloxone as soon as possible

Get into drug treatment

Getting into drug treatment reduces your risk of dying from an overdose.

[*] Available from: https://www.gov.uk/government/publications/fentanyl-preparing-for-a-future-threat/guidance-for-local-areas-on-planning-to-deal-with-fentanyl-or-another-potent-opioid [Accessed 29 Feb 2024]. *Guidance adapted under Open Government Licence v3.0.*

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