

Patient Safety Alert NPSA 2009/PSA005

Safer lithium therapy

December 2009

Supporting information

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NOTE: This supporting information is intended to be read with the Patient Safety Alert NPSA/2009/PSA005

(see: www.nrls.npsa.nhs.uk/alerts).

1. Overview

There have been deaths, severe harms and a substantial number of reports relating to lithium therapy. Analysis of errors reported to the National Patient Safety Agency (NPSA) Reporting and Learning System suggests lithium therapy is an error-prone process. Monitoring of lithium therapy is a specific issue. A recent audit demonstrates less than optimal monitoring of lithium and a failure to adequately prepare patients to recognise therapy-induced side effects or toxicity.

Monitoring, whether according to National Institute for Health and Clinical Excellence (NICE) or Quality Outcome Framework (QOF) standards is unsatisfactory. National Institute for Health and Clinical Excellence guidelines¹ describe a pattern of monitoring that is more stringent than the QOF audit standard. Maintaining patients within the appropriate therapeutic margin requires scheduled monitoring. This Patient Safety Alert supports the NICE guidance and requires that patients are monitored in either primary care, secondary care or both according to its instruction. Communication between healthcare providers is essential and may be facilitated by patient-held records.

A patient booklet, alert card and record book have been developed to support communication between healthcare providers and empower patients taking lithium. This informs patients of key aspects of their treatment including side effects and toxicity. These resources should be made available to all patients on lithium therapy and their use supported by healthcare professionals.

This Alert directs healthcare practitioners to comply with monitoring aspects of NICE guidance in relation to lithium therapy. It requires that blood test results are available at the point when clinical decisions are made. Empowering patients with a mechanism for tracking results will introduce additional safeguards on prescribing and dispensing of lithium therapy.

This supporting document provides additional understanding for implementation and supports arguments for NHS service engagement.

2. Further details of the actions recommended

2.1 Alert actions

The Alert requires,

Action by all organisations in the NHS and independent sector where lithium therapy is initiated, prescribed, dispensed and monitored.

An executive director, nominated by the chief executive working with relevant medical, nursing and pharmacy staff and the lead biochemist providing services to the trust, should put arrangements in place to ensure that **by 31 December 2010**:

1. patients prescribed lithium are monitored in accordance with NICE guidance;
2. there are reliable systems to ensure blood test results are communicated between laboratories and prescribers;
3. at the start of lithium therapy and throughout their treatment patients receive appropriate ongoing verbal and written information and a record book to track lithium blood levels and relevant clinical tests*;
4. prescribers and pharmacists check that blood tests are monitored regularly and that it is safe to issue a repeat prescription and/or dispense the prescribed lithium, and;
5. systems are in place to identify and deal with medicines that might adversely interact with lithium therapy.

* The NPSA has developed a patient information booklet, lithium alert card and record book for tracking blood levels.

In order to achieve the above, the NHS and independent organisations are recommended to take additional actions by the implementation date.

2.2 Additional actions

Additional actions are recommended to support full implementation of the Alert.

1. Patients prescribed lithium are monitored in accordance with NICE guidance,

‘that, all health care practitioners providing National Health Service (NHS) services to patients on lithium therapy are made aware of, and adhere to, the NICE monitoring guidance. The minimum requirement is for lithium blood level monitoring ‘normally’ every three months and thyroid and kidney (renal) function tests every six months. In addition, yearly health checks and monitoring of weight are recommended.

Further, that there are effective audit systems in place for those commissioning or providing services to confirm patients are in a position to benefit from monitoring.’

2. There are reliable systems in place to ensure that the results of blood tests are communicated between laboratories and prescribers,

‘that, processes and mechanisms are in place for taking patients’ blood samples, arranging for analysis of lithium blood levels and related health tests, then ensuring that the results are conveyed in a timely manner to healthcare practitioners to inform both initial and repeat prescribing.

This will require that patients’ bloods are taken in advance of clinical assessment. It is important that patients provide an accurate time between the last dose and when blood is taken. For consistent interpretation and reliability, this gap should be as close to 12 hours as possible. Wording to this effect is included in the patient information booklet.

Monitoring may occur in primary care, secondary care or both. With effective communication between providers patients should not be excessively monitored.

Further, that benchmarks for the timeliness of results being available to impact on clinical decisions are defined, agreed, monitored and implications assessed.'

3. At the start of lithium therapy and throughout their treatment patients receive appropriate ongoing verbal and written information and a record book to track lithium blood levels and relevant clinical tests,

'that, on issuing the booklet, alert card and record book (see below), the healthcare practitioner must complete the patient's details, service providers' details and current lithium therapy. The record book should be annotated with the patient's current lithium blood level, the expected upper and lower lithium blood level range and healthcare tests results.

The lithium blood level range may alter with time, and should be amended to reflect the current clinical expectation for safe and effective therapy.

To support this action, the; National Patient Safety Agency (NPSA, Prescribing Observatory for Mental Health (POMH-UK) and National Pharmaceutical Association (NPA) have produced three resources presented together in a purple folder.

I. Lithium therapy: important information for patients

Patients should receive this written information reinforced with verbal advice before the first dose of lithium is taken. It should be reinforced at hospital discharge, at the first lithium clinic appointment, and when necessary throughout the course of their treatment. Patients currently on lithium therapy should still receive this written and verbal advice.

This is a 24 page booklet with spaces for details of the patient, supporting health provider services and his/her current lithium therapy. It provides information each patient must know and understand in order to make lithium therapy safe. It has been designed to convey key messages to the target audience. This information is arranged under seven headings.

1. What is lithium and what is it used for?
2. Checks needed before you start to take lithium
3. How to take lithium
4. Blood tests after starting taking lithium
5. What side effects can lithium cause?
6. What happens if the level of lithium in my blood is too high?
7. What can make the lithium level in my blood get too high?

II. Lithium Alert Card

This is the size of a credit card. It should be carried by the patient at all times. It informs healthcare professionals that the patient is understood to be taking a specific brand of lithium and the dose. It provides details of the patient's NHS number and contacts in an emergency. Where a patient is experiencing toxic effects this information could be life-saving.

III. Record Book

This is a note-book sized, portable record of essential information on a patient's therapy, contacts, lithium blood levels and health care checks including those for thyroid function, renal function and weight changes. It is carried by a patient (or carer) and is shown to healthcare professionals to ensure clinical decisions are taken in the full knowledge of an individual patient's health status.

It should be completed on all occasions when clinical decisions are taken based on lithium blood levels and health care checks. It is complementary to the patient's record and enables healthcare professionals and patients to personally track changes in therapy. It empowers patients to engage with and be part of their own therapy.

The first entry line/row of the book has been completed with values as an exemplar. Healthcare professionals should stress to patients that these are NOT markers or target values. Patient should be told to enter the next appointment date on the next line/row as a reminder.

It should be noted that the ranges and units of thyroid function tests vary between laboratories. Prescribers and dispensers should be aware of the local reporting range for Thyroid Stimulating Hormone (TSH) and FreeT4 (FT4) plus any other reported indicators of thyroid relevant to lithium therapy. The NICE guidance stipulates monitoring of TSH.

The management of subclinical hypothyroidism remains controversial. The following approach has been suggested. If the serum TSH is confirmed to be above twice the 'normal' limit, for example a laboratory may report this situation with TSH test results above 10 mU/L, then there is a high risk of progression to overt hypothyroidism and levothyroxine should be prescribed. If the value is between 5 and 10 mU/L more frequent monitoring is indicated and a trial of levothyroxine may be appropriate particularly if the patient is symptomatic.^{2 3 4}

Further information

The responsibility for the supply of patients' booklets, lithium alert cards and record books must be with the healthcare practitioner who initiates the therapy. In most cases this will be the consultant psychiatrist. Where a patient is being started or maintained in the community, the responsibility is with the patient's general practitioner. Supply may also be through the local community pharmacy.

Confirmation that the patient has received written information reinforced with verbal advice and that the necessary details have been transferred to the booklet, alert card and record book must be noted in the patient's healthcare record.

Where drug therapy is changed, for example the dose is altered, this should be reflected as soon as is practical in the record book, booklet and alert card. Variation of drug therapy details between the record book, booklet and alert card is a patient safety issue and must be reconciled.

Electronic copies of the purple booklet in English and Welsh are available at www.nrls.npsa.nhs.uk/.

Supplies of these new items will be available from December 2009, from the current NHS Non-Secure Contract held by 3M. Orders should be sent to

Telephone: 0845 610 1112

Email: nhsforms@spsl.uk.com

If you have access to the electronic ordering system 'Astroweb', you can place your orders this way. This contract is managed by Kay Ellermeyer, National Programme Manager, NHS Non-Secure Forms. You can contact her on 01244 650458 or email kay.ellermeyer@wcheshirepct.nhs.uk .'

4. Prescribers and pharmacists check that blood tests are being monitored regularly and that it is safe to issue a repeat prescription or dispense the prescribed lithium,

'that, as a safeguard, prescribing and dispensing of lithium prescriptions should be on the bases that NICE guidelines for monitoring are being followed. Also, that current values and test result trends are safe as they relate to each patient's health status.

Standard Operating Procedures (SOPs) and policies should describe clear processes and audit benchmarks for both prescribing and dispensing that must be adhered to if patient safety is compromised.

As a principle, therapy should not be withheld.

Where it is not possible to assess monitoring, the pharmacist responsible for dispensing a prescription (or making an emergency supply), should

communicate to the prescriber that lithium medication has been provided without blood test data being available.

In the case of prescribing by a GP or a clinician/consultant, arrangements for blood tests should be made as soon as possible. Communication should occur between the GP and clinician/consultant that therapy was initiated without blood test data.

The written information for patients informs them that healthcare professionals like community pharmacists will ask them for their record book to confirm that it is safe to dispense further supplies of their medicine.'

5. Systems are in place to identify and deal with medicines that might adversely interact with lithium therapy,

'that, SOPs, decision support systems, patient medication records, patient records, inpatient charts, medication administration records reflect the need to identify and deal with potential interacting medicines, whether on prescription or brought over-the-counter.

There must be effective communication between all healthcare practitioners involved with patients on lithium therapy. This will ensure the impact of interacting medicines is considered when clinical decisions are made.

While many medications have been reported as interacting with lithium,⁵ this monitoring must highlight as a minimum the potential for lithium's interactions with the following commonly prescribed therapies and OTC medicines:

1. thiazides and related diuretics;
2. ACE inhibitors
3. non-steroidal anti-inflammatory drugs (NSAIDs); and,
4. sodium bicarbonate containing, non-prescription antacids or urinary alkalinising agents.'

This guidance does not override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or carer.

3. Background

3.1 Lithium therapeutics and monitoring

Lithium is used clinically for:

Bipolar disorder,

- the acute treatment of mania. The effectiveness of lithium appears to reduce with over 10 previous manic episodes or rapid cycling mania,
- bipolar depression. Guidelines are unclear due to current lack of evidence but suggest that antidepressants are of limited utility and recommend optimisation of mood stabilisers such as lithium,
- Prophylaxis. First line for 6 months then in combination; and,

Unipolar depression,

- treatment of refractory depression, although recent studies appear less able to support lithium over placebo, guidelines currently support the use of lithium, and the evidence suggests this is most effective in combination therapy, and may decrease suicidality.

Its use for these indications is supported by the 2006 NICE guidelines for depression and bipolar disorder and the British Association for Psychopharmacology.⁶ For most patients, lithium is a long-term treatment. For example it is recommended that patients with bipolar disorder take lithium for at least three years.⁷

Lithium has a narrow therapeutic range necessitating blood levels between 0.4-1.2mmol/L;⁸ The lower end of this range is used for elderly and infirmed patients and the upper end for younger patients, particularly those being treated for an episode of mania. It is entirely possible for an elderly patient at the upper limit to experience toxicity.

The NICE guidance is that when initiating long-term treatment, clinicians should aim for levels of 0.6-0.8 mmol/L, with higher levels possibly being of benefit for patients with predominantly manic symptoms.¹

If the concentration of lithium in the blood is too high, blurred vision, muscle weakness, coarse tremor, slurred speech, confusion, seizures and renal damage may all occur. Lithium treatment increases the risk of clinical hypothyroidism up to five-fold, the risk being particularly high in women who are 40-59 years old.⁹ The clinical symptoms of hypothyroidism overlap with those of depression and may therefore remain undiagnosed and untreated unless specific screening tests are undertaken.

Lithium kinetics are as follows; $t_{1/2}$ 12-27 hours increasing to 36 in the elderly with decreased renal function,¹⁰ $t_{1/2\alpha}$ absorption 2-3 hours, 80-100% bio available, no first pass, not protein bound, V_d approximating body water, not metabolized, clearance $t_{1/2\beta}$ 16 to 36 hours. Dosage of the carbonate salt is commonly 200 to 400 mg once daily at night, giving steady state levels after 5 to 7 days of 0.4 to 0.8 mmol/L in a 'normal' patient.

With this kinetic profile, dosing can be adjusted based on blood levels and renal function. Conversely lithium is affected by changes in kidney (renal) function and fluid balance¹¹

and altered fluid compartmentalisation such as seen in obesity¹² and in pregnancy where increased dosage may be appropriate.

Medicines such as ACEi, thiazide diuretics, non-steroidal anti-inflammatory drugs¹³ and sodium containing antacids, affect kidney function and lithium excretion. Unless lithium levels are monitored and the dose adjusted, concomitant use may cause lithium toxicity or with sodium containing antacids sub-therapeutic levels.

It is recommended that lithium blood levels are taken at least 12 hours after the last dose.¹⁴ As lithium follows a two compartment model, this circumvents the large patient variability of blood concentrations seen in the alpha distribution phase and allows for reproducible and clinically meaningful lithium blood levels.¹⁵ It is important that the exact time between the last dose and taking blood for lithium levels is known. The longer this time exceeds 12 hours the more difficult and less reliable the pharmacokinetic interpretation. This is especially important when trying to rationalise lithium blood levels and clinical indications of toxicity.

3.2 Lithium prescribing

Treatment with lithium is usually initiated and stabilised by consultant psychiatrists who work with clinical teams to monitor the patient’s clinical condition at periodic clinic appointment. However, general medical practitioners and community pharmacists are mostly responsible for prescribing and dispensing respectively prescriptions for lithium.

In England for the year 2008 the Prescription Pricing Directorate reimbursed 824,900 prescriptions for lithium carbonate in tablet formulation and 1,800 for the citrate salt as a liquid.¹⁶

The current QOF awards payment under Mental Health is as follows (table 1):

Table 1: QOF Mental health indicators

Indicator	Points	Payment Stages
MH9 the percentage of patients with schizophrenia, bipolar affective disorder and other psychoses with a review recorded in the preceding 15 months. In the review there should be evidence that the patient has been offered routine health promotion and prevention advice appropriate to their age, gender and health status.	23	40%-90%
MH4 The percentage of patient on lithium therapy with a record of serum creatinine and TSH in the preceding 15 months.	1	40-90%
MH5 The percentage of patients on lithium therapy with a record of lithium levels in the therapeutic range within the previous six months.	1	40-90%

These audit standards do not follow the NICE guidance.

4. Triggers for action

4.1 National Health Service Litigation Authority (NHSLA)

Directly related to lithium treatment NHS Litigation Authority between 1995 and 2004 recorded 16 cases, two fatalities, 12 severe harms with claims of over £2 million paid by the Clinical Negligence Scheme for Trusts (CNST),

4.2 Medical Defence Union

Since 1996, 15 were directly related to lithium toxicity and monitoring

4.3 National Patient Safety Agency

The NPSA has been aware of preventable harm from the use of oral lithium treatment for bipolar disorder for some time. A review of the available evidence was conducted which demonstrated that wrong or unclear dose or strength and monitoring were key issues for lithium therapy.

A search of all medication incidents reported to the NRLS (National Reporting and Learning System) relating to Lithium was carried out between November 2003 to 9 December 2008. It is this data set that informed a POMH-UK audit.¹⁷

This included a free text search under the category 'medication' of the following terms: Lithium, Camcolit, Liskonium, Liskonum, Priadel, Li-Liquid and Liliquid.

Quantitative analysis

A review of medication incidents related to the use of lithium reported to the RLS identified a total of 567 incidents. The majority of these incidents were submitted from within mental health services (Table 2)

Table 2: Care setting

Care Setting	Total
Mental health service	317
Acute / general hospital	160
Learning disabilities	32
Community nursing, medical and therapy service (including community hospital)	30
Community Pharmacy	23
General practice	5
Total	567

Of these 567 incidents it was identified that two of those resulted in 'severe' harm to the patient, although the majority were reported as 'no harm' events (Table 3).

Table 3: Degree of harm

Degree of Harm	Total
Death	0
Severe	2
Moderate	34
Low	61
No harm	470
Total	567

Death and severe incidents have been validated

A further analysis of the RLS data allowed a breakdown by 'Stage in the medication processes.' This identified that the 'administration' and 'prescribing' phases of the process are the most prone to error (Table 4) according to reports submitted to the RLS.

Table 4: Stage of the medication process

Stage During Medication Process	Total
Administration / supply of a medicine from a clinical area	279
Prescribing	115
Preparation of medicines in all locations / dispensing in a pharmacy	107
Monitoring / follow-up of medicine use	27
Other	29
Advice	10
Total	567

By analysing the data further, a breakdown can be made showing the type of error that has been reported. As can be seen by the data in Table 5: Medication error type (page 12) 'wrong dose or strength' was the most commonly reported error type. This is consistent with all medication data submitted to the RLS.

Table 5: Medication error type

Medication error type	Number
Wrong / unclear dose or strength	124
Wrong frequency	77
Omitted medicine / ingredient	71
Wrong drug / medicine	74
Other	70
Wrong quantity	46
Mismatching between patient and medicine	29
Contra-indication	23
Wrong / transposed / omitted medicine label	11
Wrong storage	6
Wrong formulation	7
Adverse drug reaction (when used as intended)	9
Wrong / omitted / passed expiry date	8
Unknown	5
Wrong method of preparation / supply	4
Wrong / omitted patient information leaflet	2
Wrong / omitted verbal patient directions	1
Total	567

Examples of medication incident reports

1. Lithium level of 0.97mmol/L treated as normal in a 61 year old with symptoms of lithium toxicity, as this fell within the local lab range of 0.6-1.2 mmol/L. The patient later developed life threatening toxicity and renal failure.
2. Emergency admission of patient for lithium toxicity in a critical condition. Unfortunately his lithium levels were out of date. The last level (5 months old) was within the therapeutic range, hence his lithium was re - authorised. Unfortunately, it appeared his out-patient appointments had been subject to cancellations hence his lithium levels were not being regularly monitored. Patient at time of report was being ventilated.
3. Patient on treatment for depression with lithium which was monitored by his GP. The lithium level had gone up but it was still within therapeutic levels (but may have been toxic for him). He had a stroke and died as a result but his clinical state may have been worsened by the effects of a high lithium level. The concern was that if the lithium level is not above normal it is not flagged up on the system even though it may have doubled in reality.
4. Patient was seen in community and was diagnosed with Lithium toxicity. Lithium levels were three times higher than last time they were checked, and well above therapeutic range. On discovering patient blood results, patient was immediately transferred to A&E before transferring her to the Medial Admissions Unit for treatment for renal failure.

5. Patient on lithium for many years. Discharged on diuretic but lithium dose was not reduced. Readmitted three weeks later with life threatening lithium toxicity. Lithium levels are increased when diuretics are introduced

4.4 **The Royal College of Psychiatry, Prescribing Observatory for Mental Health (POMH-UK)**

As one of its central topics this group audited the use of lithium and proposed guidance to minimise harm. It produced a baseline report for the Trusts that responded. Thirty-five trusts submitted their retrospective analyses of 3373 patient notes by 436 clinical teams representing approximately 6 per cent of patients taking lithium for over one year in the UK. For 2976 patients full data was available. The following table (Table 6: Adherence with lithium monitoring, page 14) summarises the findings relative to QOF and NICE guidelines adherence during maintenance treatment.

These results indicate a lower monitoring frequency than implied by 8,294 GP practices submissions to QOF indicating 91.3 per cent and 83.9 per cent of total points achieved for MH4 and MH5 respectively¹⁸ (see Table 1: QOF Mental health indicators, page 9).

Of the 397 patients identified who had been treated for less than a year (Table 7: Initiation of treatment, page 14) there was documented evidence that patients had NOT been informed of critical information to ensure safe and effective use of medication. Specifically over half of patients were not prepared to recognise toxicity or to avoid risks that might lead to toxicity. No account was taken of age-related increased risks.

Table 6: Adherence with lithium monitoring

Number of tests in last year	U&Es	Creatinine	Thyroid function tests	Weight/ BMI/waist circumference	Serum lithium
0	484 (16%)	553 (19%)	524 (18%)	2155 (72%)	273 (9%)
1	780 (26%)	795 (27%)	976 (33%)	416 (14%)	668 (22%)
2	598 (20%)	592 (20%)	693 (23%)	155 (5%)	572 (19%)
3	472 (16%)	466 (16%)	453 (15%)	90 (3%)	561 (19%)
4	346 (12%)	313 (11%)	208 (7%)	62 (2%)	503 (17%)
5 or more	296 (10%)	257 (9%)	122 (4%)	98 (3%)	399 (13%)

Legend





	Neither QOF nor NICE Standard met
 + 	Meets QOF standard
	Meets NICE guidelines

Table 7: Initiation of treatment

During treatment initiation in the last year, the patient <u>was</u> informed of the following:	n
1. Side effects of lithium	244 (62%)
2. Signs and symptoms of lithium toxicity	178 (45%)
3. Risk factors for lithium toxicity	166 (42%)

5. Further support

The NPSA has ongoing development of support for implementation as follows:

- A SOP with the National Pharmaceutical Association for community pharmacy;
- A Service Level Agreement template for laboratory services and communications between healthcare providers;
- Ongoing discussions to ensure the QOFIT solutions for communication and Alerts; and,
- Ongoing work with to align the QOF standard with NICE guidance.

6. Compliance checklist

All organisations in the NHS or independent sector should use the checklist below to assess compliance with the *Safer lithium therapy* Alert. When all actions have been completed, the guidance can be considered to be fully implemented. Compliance with all actions is necessary to ensure safe lithium prescribing.

Table 8: Compliance checklist

Action Number	Recommendation	Required Action	Compliance
1	Patients prescribed lithium are monitored in accordance with NICE guidance.	a) Local clinical policies and procedures must include a requirement to follow current NICE monitoring guidelines for lithium therapy.	a) Yes/No
		b) An annual audit system is in place to review monitoring of lithium therapy.	b) Yes/No
2	There are reliable systems in place to ensure that the results of blood tests are communicated between laboratories and prescribers;	a) Plans or systems are in place to effectively communicate blood test results as recommended by NICE between laboratory services and prescribers in primary and/or secondary care.	a) Yes/No
		b) An annual audit system is in place to monitor timeliness of communication against agreed benchmark standards	b) Yes/No
3	At the start of lithium therapy and throughout their treatment patients receive appropriate ongoing verbal and written information and a record book to track lithium blood levels and relevant clinical tests.	a) Local policies and procedures specify the requirement to issue and support the use of the new lithium booklet, alert card and record book.	a) Yes/No
		b) An annual audit system is in place to confirm that patients receive the lithium booklet, alert card and record book.	b) Yes/No
		c) An annual audit system is in place to confirm that patients carrying the record book have up-to-date records of blood test results and health checks	c) Yes/No

4	Prescribers and pharmacists check that blood tests are being monitored regularly and that it is safe to issue a repeat prescription or dispense the prescribed lithium	<p>a) Local policies, procedures and SOPs direct prescribers and pharmacists to check the scheduling of blood tests, then to reassure themselves before prescribing or dispensing that, given the test results, no patient harm will result.</p> <p>b) Where patients are unwilling to accept and use a record system for personal monitoring, and it is not possible to otherwise perform this check, that the local policy, procedure or SOPs stipulates how to manage the consequence(s).</p> <p>c) An annual audit system is in place to monitor the checking process and to identify where this has not been possible.</p>	<p>a) Yes/No</p> <p>b) Yes/No</p> <p>c) Yes/No</p>
5	Systems are in place to identify and deal with medicines that might adversely interact with lithium therapy.	<p>a) Local policies, procedures and SOPs direct healthcare practitioners to communicate and take account of possible changes in lithium levels when interacting medicines are identified.</p> <p>b) An annual audit system is in place to monitor communications and subsequent actions where clinically important interactions are identified.</p>	<p>a) Yes/No</p> <p>b) Yes/No</p>

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2 secondary care. *Clinical Guideline* 38, 2006. www.nice.org.uk
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