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Howkins, J

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## Community Monitoring of Health Parameters in People with Intellectual Disabilities Prescribed Lithium

Joshua Howkins<sup>a</sup>, Mike Wilcock<sup>b</sup>, and Rohit Shankar <sup>a,c</sup>

<sup>a</sup>Cornwall Intellectual Disability & Epilepsy Research (CIDER) Centre, Cornwall Partnership NHS Foundation Trust, Truro, UK; <sup>b</sup>Royal Cornwall Hospital Trust, Truro, UK; <sup>c</sup>University of Exeter Medical School, Truro, UK

### ABSTRACT

**Background:** Lithium is well described in managing certain mental illnesses including in people with intellectual disabilities (ID). It requires regular monitoring particularly of serum levels and relevant biochemistry. However, existing monitoring protocols do not provide ID-specific guidance leading to increased risk of poor-quality care. This study aims to construct a protocol to aid monitoring in primary care in this cohort. Need for a protocol is further explored by retrospectively auditing monitoring standards in people with ID in Cornwall, UK, and confirming gaps in current practice which may be minimized with clearer guidance.

**Methods:** Protocol was developed drawing on existing guidance for the general population and considering challenges and best practice associated with monitoring in people with ID. The protocol was applied as an audit to all people with ID currently on lithium on the GP ID register across all GP practices in the county of Cornwall, UK, to explore current standards of monitoring to help elucidate whether increased guidance may be of use.

**Results:** A novel protocol was developed and supplemented with additional information which is hoped to provide a useful reference guide in primary care. During audit, nine of the ten people with ID receiving prescriptions for lithium across the county were identified and data collected. Audit showed monitoring was to a reasonably high standard, though blood tests and annual health checks were not always performed within preferred maximum timeframes.

**Conclusions:** This protocol represents the first ID-specific approach for monitoring lithium and associated health parameters in primary care. Auditing against the protocol showed gaps in current standards of care which may indicate a need for clearer published guidance. Some groupings of results highlighted particular areas of need. We hope that clear protocols, such as ours, may aid safe and timely monitoring of lithium treatment in future.

### KEYWORDS

Community; monitoring; lithium; intellectual disability

## Background

Lithium is well described in managing certain mental health conditions and effective in treating bipolar disorder and recurrent depression (Abou-Saleh et al., 2017; Severus et al., 2014; Undurraga et al., 2019). In people with ID, it

**CONTACT** Rohit Shankar  Rohit.shankar@nhs.net  Chy Govenck Threemilestone Industrial Estate, Truro, Cornwall TR4 9LD, UK.

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may also be used to help manage agitation and aggression (Craft et al., 1987; Worrall et al., 1975).

However, there is concern about the over-use of psychotropic medication in people with ID, both for psychiatric diagnoses and in “off label” prescribing, and the high burden of polypharmacy (Branford et al., 2019; McMahon et al., 2020; Sheehan et al., 2015). In recent years particularly, the UK Government has committed to improving the use of psychotropic medication in people with ID, as encapsulated in the STopping Over Medication of People with a learning disability, autism, or both program (STOMP) (Shankar et al., 2019). Although not included in STOMP, lithium has a well-documented adverse effect profile and narrow therapeutic window and commands a significant burden of monitoring on patients and the healthcare system (National Patient Safety Agency, 2009).

Guidance on prescribing and monitoring lithium in the general population exists both nationally and locally in the UK (Joint Formulary Committee, 2019; Royal Cornwall Hospitals NHS Trust, 2019; SPS et al., 2017; Taylor et al., 2018). However, even with this clear guidance, full monitoring compliance has been found to be substandard (Nederlof et al., 2019). No specific national guidance exists for the ID cohort which may present an additional source of uncertainty around monitoring and increase the risk to patients (De Leon, 2012).

Monitoring of drug treatment is important in this cohort for a number of reasons. People with ID can be more likely to react adversely to medications or at lower doses than the general population (Pary & Hurley, 2006). This issue is compounded by the higher burden of co-morbidity and polypharmacy often observed (Kinnear et al., 2018), which has been shown to lead to higher rates of premature mortality (Heslop et al., 2014). Adverse effects may be masked or present only through a change in behavior (Pary & Hurley, 2006; Valdovinos et al., 2005) and people with ID may struggle to seek help for adverse effects due to communication difficulties (Lindsay et al., 2020), an issue compounded by the possibility of diagnostic overshadowing which can delay or undermine proper investigation and management (Lindsay et al., 2020).

Considering lithium specifically, many body systems can be negatively affected, especially with chronic use (Joint Formulary Committee, 2019; Shine et al., 2015; Toxbase, n.d.).

Rapid review of the literature on the use of lithium in people with ID highlights evidence of multi-system adverse effects in a pattern largely homogenous with those experienced by the general population (Canan et al., 2008; El-Bakush et al., 2014; Janowsky et al., 2011, 2009; Pary, 1991; Pirotte et al., 2008; Worrall et al., 1975). Both reversible and irreversible issues were noted though Janowsky et al. in 2009 and 2011 highlight the potential for chronic kidney damage to occur.

In people with ID, lithium toxicity may occur at serum levels considered therapeutic in the general population (Andrade et al., 1988; Maruta, 2003; Otsuka et al., 2012; Soni, 2019). Additionally, there are many examples

highlighting the disproportionately high burden of polypharmacy in this group (El-Bakush et al., 2014; Hadley et al., 1989; Takahashi et al., 2000; Valdovinos et al., 2005). Together, these add weight to the need to achieve regular monitoring and to reduce over-prescribing, a key tenet of STOMP and current clinical practice.

Behavior change being the sole or primary change noted in a patient experiencing lithium-related adverse effects is evidenced clearly (Hadley & Cason, 1989; Maruta, 2003; Nishikawa et al., 1992; Takahashi et al., 2000; Valdovinos et al., 2005). The difficulty that clinicians may encounter in assessing and monitoring patients is described in the literature, with evidence presented of methods to increase engagement between healthcare providers and service users to help empower patients and reduce diagnostic overshadowing (Bhaumik et al., 2007; Buckley & Sharrard, 2003; Clarke & Pickles, 1994; ; Pary & Hurley, 2006; Paton et al., 2011).

Significant potential for uncertainty, overshadow and subsequent harm is evident from the above. Therefore, we suggest that bespoke and clear guidance on monitoring is vital to aid primary care physicians in prescribing safely, and to patients in allowing full consideration of treatment options.

Due to this need and the current gap in guidance for the explicit health needs of people with ID, this paper aims to develop and pilot an ID-specific protocol for the monitoring of lithium and associated health parameters in primary practice. Pilot will take the form of a small audit of our service area to assess feasibility.

## Methods And Materials

Relevant national and local guidance on lithium prescribing was sourced in November 2019 (Joint Formulary Committee, 2019; National Collaborating Centre for Mental Health, 2014, ; Royal Cornwall Hospitals NHS Trust, 2019; SPS et al., 2017; Taylor et al., 2018) to provide a base upon which to structure our novel ID-specific protocol. These guidelines are listed in (Table 1) along with extracted key points for monitoring.

Our protocol (Figure 1) was brought together through discussion of this selected literature review amongst our panel of psychiatrists and pharmacists, assessing the evidence base for alterations or additions to the monitoring requirements for the general population. The summary of evidence used for the protocol formation is presented in (Table 2).

The devised protocol (Figure 1) formed the basis for a countywide pilot audit into the monitoring of lithium treatment and associated health parameters in people with ID in the county of Cornwall, UK (pop:538,000).

The core monitoring parameters utilized for the audit were serum lithium levels and other key blood tests (full blood count, electrolytes

**Table 1.** Key sources for national guidance on prescribing and monitoring lithium.

Source	Summary of monitoring requirements
BNF (Joint Formulary Committee, 2019)	Pre-treatment: BMI; cardiac; electrolytes; FBC; renal; thyroid. ECG if risk factors. During treatment: BMI; electrolytes; eGFR; plasma levels; thyroid function.
Maudsley prescribing guidelines (Taylor et al., 2018)	Pre-treatment: BMI; cardiac function; renal; thyroid. ECG if risk factors. During treatment: eGFR; plasma levels; thyroid function.
SPS guide for monitoring in primary care (SPS et al., 2017)	Pre-treatment: BMI; electrolytes; FBC; renal; thyroid. ECG if risk factors. During treatment: annual health review (including blood pressure); BMI; plasma levels; thyroid.
NICE guidelines for bipolar disorder (National Collaborating Centre for Mental Health, 2014)	Pre-treatment: BMI; calcium; electrolytes; eGFR; FBC, thyroid. ECG if risk factors. During treatment: BMI; calcium; plasma levels; renal; thyroid function.
NICE guidelines for depression (National Collaborating Centre for Mental Health, 2010)	Pre-treatment: renal and thyroid function During treatment: plasma levels; renal; thyroid function. ECG if risk factors.

Abbreviations: BMI (basal metabolic index); ECG (electrocardiogram); eGFR (estimated glomerular filtration rate); FBC (full blood count).

and kidney function, thyroid function, and calcium) within the previous 6 months and annual health check within the previous 12 months. Audit registered with Cornwall Foundation NHS Trust clinical audit department reference 619;02/2020, results displayed in (Table 3).

Anonymized patient data were gathered by first searching ECLIPSE LIVE (which securely accesses patient data from general practice (GP) computer systems, in a non-identifiable report) to facilitate identification of practices with patients meeting our criteria (current lithium prescription in any form and diagnosis of learning disability, intellectual disability, or unspecified disorder of scholastic skills). Individual practices where the persons were identified were then contacted. Data was requested and audited only for the key monitoring factor timeframes (blood tests six months and AHC twelve months as above) in people matching the specified cohort to preserve anonymity. Audit results were noted in tabular format as either success or failure based on the criteria being met and within the expected specified timeframe (Table 3).

## Results

### *Construction of the Protocol*

In devising the ID-specific monitoring protocol (Figure 1), we considered the evidence as described in the introduction for implications on the regimen for monitoring health parameters, above guidance for the general population (Table 1). For comparison, key features of this guidance are (when amalgamated): weekly lithium levels on initiation and with dose adjustments until stable, trending

**Monitoring protocol for lithium and associated health parameters in people with**



**Figure 1.** Proposed standard for monitoring with additional educational information contained for healthcare worker and patient benefit.

to 6-monthly once chronically stable; baseline full blood count, calcium, renal function, thyroid function and BMI; and 3-monthly calcium, renal function and thyroid function, trending to 6-monthly for long-term monitoring, with increased regularity if concern.

**Table 2.** Summary of evidence used in formation of protocol (Figure 1).

Source	Summary of key information	Section of protocol informed
Andrade et al. (1988) Case report	Neurotoxicity developed at plasma levels considered normal for general population. Hypothesis presented that the subject's intellectual disability was a predisposing factor for this.	Initiation of treatment and serum lithium levels. No change made to protocol as current best guidance is the target range specified. In the UK, lithium is only initiated under specialist supervision and all individuals should be closely monitored during periods of dose adjustment.
Canan et al. (2008)	Initiation of lithium therapy unmasked previously unknown cardiac abnormality resulting in arrhythmia which disappeared after discontinuation and dialysis.	No change to protocol as, although population may be at increased risk of cardiac abnormality, common accessible investigations were not felt to be sensitive enough for screening purposes.
El-Bakush et al. (2014) Case report	Missed diagnosis for two weeks of lithium toxicity following dose increase resulting significant morbidity.	Lithium plasma level schedule (weekly until stable).
Hadley et al. (1989) Case report	Burden of polypharmacy: addition of fluoxetine to otherwise established lithium therapy resulted in lithium toxicity and mania.	Additional advice section. Lithium's propensity to interact with other medications is well known and a list would not be exhaustive.
Janowsky et al. (2009) Retrospective case-control	Lithium shown as an independent risk factor for renal failure.	6-monthly renal function testing. Although renal function did not return to normal levels on treatment cessation, the insidious nature of lithium-related renal failure was felt to be covered by current 6-monthly guidance.
Janowsky et al. (2011) Retrospective case-control	Long term lithium use is a risk factor for chronic renal insufficiency. No recovery in baseline eGFR after cessation of lithium	6-monthly renal function testing. As above.
Maruta (2003) Case report	Missed diagnosis and late presentation of lithium toxicity in patient presenting with weight loss.	Annual health check; BMI.
Nishikawa et al. (1992) Case report	Lithium use, particularly in combination with other psychotropics, leading to diabetes insipidus characterized by compulsive drinking.	Not explicitly stated in protocol; discussed in paper as covered by clinical responsibility to investigate acute behavioral changes.
Otsuka et al. (2012) Case report	Unusual presentation of nephrogenic diabetes insipidus as a result of chronic lithium use. Polydipsia only noted through change in behavior: client seen to be drinking from faucet.	As above.
Pary et al. (1991) Cohort	Assessment of adverse effect profile in lithium use. 58 week follow up revealed 67% of subjects reporting adverse effects.	As above.
Pary et al. (2006) Qualitative, mixed	Discussed challenges in recognition of psychotropic medication adverse effects in this cohort.	As above.
Pirotte et al. (2008) Case report	Lithium unmasking cardiac abnormality in individual with no previous abnormal cardiac history.	Pre-treatment investigations would have been unlikely to prevent this so no additions made to protocol as per Pirotte et al.: "certain drugs or medical conditions can unmask the Brugada syndrome in a patient with previously normal ECGs and no cardiac history" Also see entry for Canan et al. (2008).
Soni (2018) Case report	Unusual presentation of neurotoxicity secondary to lithium use, with therapeutic serum levels. Misdiagnosed as dementia for 18 months	Serum lithium level frequency and presumption of ad hoc clinical investigation due to change in behavior.

*(Continued)*

**Table 2.** (Continued).

Source	Summary of key information	Section of protocol informed
Takahashi et al. (2000) Case report	Co-administration of levofloxacin resulting in lithium toxicity in previously established therapy.	Additional advice section. As per Hadley et al. (1989).
Worrall et al. (1975) Randomized controlled trial	High incidence (25%) of neurotoxicity in small RCT of lithium for symptoms of aggression.	Serum lithium level frequency. Also felt clinically captured due to UK policy of lithium only being commenced under specialist supervision.
Valdovinos et al. (2005) Retrospective, qualitative	Assessed range of reported adverse effects. Noted difficulty in discriminating between change in behavior due to mood fluctuation or medication adverse effect.	As per Nishikawa et al. (1992).

Sources in Table 1 were pivotal in providing information for all parts of the protocol. The following sources provided evidence which supplemented this, allowing consideration of changes specific to needs of the ID population.

**Table 3.** Results of audit against concordance with monitoring protocol for nine patients (one per row) “□” indicates patient found to have testing within pre-defined timeframe whilst “X” indicates absence.

	Full blood count	Electrolytes and eGFR	Thyroid function	Calcium	Lithium level	Annual health check
Patient 1				X		
Patient 2	X			X		
Patient 3						
Patient 4						
Patient 5	X	X	X	X		X
Patient 6						X
Patient 7						
Patient 8						
Patient 9				X		

Considering lithium level monitoring, it was felt that general guidance should suffice for safe monitoring in our population, if properly adhered to. There is no conceivable need for monitoring more than once weekly outside of the emergency inpatient setting. Therefore, guidance was maintained at weekly until stable, trending through 3-monthly to 6-monthly when the clinician is satisfied of chronic stability. Frequency should increase in times of clinical concern or physiological change, trending back through the above pattern as the situation settles.

Considering the other health parameters, baseline blood test investigations overall were proposed to remain the same. Prescription of lithium is generally reserved for those in good or at least stable health. Patients with significant comorbidities should be reviewed on an individual basis for suitability of treatment and these cases cannot be covered by the scope of a generalized monitoring protocol. Regular serum monitoring three monthly trending toward six monthly, with evidence of stability remains safe and practical, if adhered to. Inherent within this recommendation is the provision that clinicians should increase monitoring in the acute setting as guided by the clinical picture.

Key to this decision is that monitoring frequency must strike a balance between patient acceptability, healthcare capacity and clinical necessity. It is

not practical for guidance to demand overly frequent monitoring, and a balance must be struck. Evidence for system-specific adverse effects is already well documented and tends to present over mid- to long-term rather than immediately. Therefore, it was felt to be of no clinical benefit to suggest increasing the standard monitoring frequency of the serum markers as already defined for the general population. Disruption to normal physiological processes and parameters due to acute illness or injury is a different matter and, once again, we expect the clinician to utilize clinical judgment when considering investigations in the acute setting.

The diverse nature in which adverse effects may present in our population, and the noted potential difficulties in expressing these, was felt to represent a requirement for particularly close care, distinct from patient needs in the general population. On discussion, it was felt that if concerns were raised in the community of an acute physical or behavioral change, a healthcare professional would be expected to rapidly assess the concerned person. Many areas have ID-specific services in addition to GPs, family doctors and hospital emergency departments. Therefore, acute change is more likely to be assessed as part of standard care than it might be for the general population. Reminder of the increased need of in-person assessment of acute changes when a patient is prescribed lithium was inserted into the protocol as a result of this discussion. Due to this enhanced ad hoc clinical assessment, it was not recommended to increase the advice for formal, regular biochemical monitoring in the protocol, with it felt preferably performed on an individualized basis in order to limit the burden of monitoring on stable patients.

All people with ID in the UK should receive an annual health check (AHC). This broad assessment covers many of the wider issues that are of particular importance in lithium treatment including medication reviews, weight and baseline physical observations and behavior and mental health review. Therefore, attendance of this review is vital to the ongoing assessment and optimization of health, and of the ongoing assessment of suitability for lithium treatment.

Note was made of the support in the evidence and anecdotally for increased patient and carer empowerment and for more structural guidance for GPs. In the advice box it has been made explicit to ensure mental capacity for informed consent for various decisions especially interventional ones given the cognitive and communicative vulnerabilities of people with ID. Where there is a lack of mental capacity identified as per the Mental Capacity Act 2005 UK or similar guidance due best interest process needs following. This protocol is hoped to go some way toward providing that support by supplying clear guidance to follow. Due to this, additional information was inserted onto the monitoring sheet in boxes so that the protocol could also be used to clarify advice and requirements as necessary, providing a reference frame for clinical review above its baseline role as a protocol for monitoring.

## **Audit Results**

The pilot audit identified ten people with ID prescribed lithium in Cornwall. Of these ten people, full required data on monitoring was accessed for nine (Table 3). The tenth person was unable to be uncovered in GP records. It is unclear whether this was due to improper coding, unknown variations in coding between systems or inadequate information being provided due to the anonymized nature of the data.

All patients had received serum monitoring of lithium levels within the timeframe recommended by protocol for long term management (6 months). Most other serum markers were similarly well accounted for, though trends were offset by patient 5 having not received testing for any markers other than lithium level. Aside from results pertaining to patient 5, serum markers were obtained within the 6-month timeframe for all markers other than full blood count in one patient (patient 2), and calcium markers in 3 patients (patients 1, 2 and 9). Annual health check was performed within the past year in all patients other than patients 5 and 6.

## **Discussion**

### ***Discussion of the Protocol***

We were satisfied with the final protocol, believing it covers relevant markers and provides a safe yet practical guidance for monitoring in the stable setting. We hope that the supplementary boxes “additional advice” and “signs of toxicity” complement the protocol to allow a reference for primary care of additional factors that must be remembered when responsible for lithium prescriptions in people with ID.

### ***Discussion of Pilot Audit Results***

Audit highlighted some notable trends in the current monitoring of lithium in people with ID in the community (Table 3), which we believe highlight the requirement for a protocol such as this.

Calcium testing is the most frequently neglected (for four out of nine patients within our 6-month timeframe). It is felt that this is potentially due to the wording of current national advice from the British National Formulary (Joint Formulary Committee, 2019). Calcium is grouped with “electrolytes” in documentation but not practically recognized as such: most UK biochemistry ordering systems have separate order sets for “urea and electrolytes” (including sodium, potassium, urea and creatinine only) and for calcium (or sometimes “bone profile”). Inconsistencies such as this are potentially a source of shortcoming which should be resolved by having one clear monitoring protocol available.

Lack of AHC completion is a source of concern. Every person with ID should have a regular, yearly AHC in addition to any suitable acute physical health monitoring including, where appropriate, relevant biochemistry. This is of particular importance in the setting of chronic physical conditions and long-term psychotropic medication use. It is of highlighted importance by the Learning Disability Mortality Review (LeDeR) program and leads to a proven reduction in mortality (Heslop et al., 2014; Kennedy et al., 2019).

A further notable concern is of the one participant in the audit having refused all monitoring interventions other than plasma lithium level in the past year, implying that blood was taken but that either other investigations were refused by the patient or not requested by the GP. If a patient cannot be relied upon to fulfil the requirements of safe practice, it should be assessed whether lithium is suitable for them or whether an alternative is preferable. Capacity to consent to treatment is not a static concept and should be reviewed if a patient (and if appropriate their next of kin or legal appointee) is unwilling or unable to fulfil the requirements for safe treatment or if attendance at monitoring reviews lapses over time. If this lapse in monitoring is instead due to a lack of awareness by the GP, again is it hoped that provision of a clear monitoring protocol may improve concordance to safe monitoring practice.

### **Limitations of the Paper**

Taken together, the additional value of this revised protocol cannot be fully supported by the evidence provided in this manuscript; for that a direct comparison of old and new protocols in a larger sample size would be required. Whilst the rapid literature review allowed informed deliberation on modifications to monitoring guidance for the general population, the protocol cannot be taken as drawing fully from all possible evidence as a systematic review of the literature did not take place. English language only and limited databases were searched and thus the provision of evidence to the panel suffers from an amount of structural bias. In addition to this, sources of evidence were not individually appraised or critiqued, meaning that information drawn from them cannot be relied upon as high quality. Withstanding these potential biases, the regimen recommended by our ID-specific protocol does not vary substantially from that for the general population. The only additional factors are reminders to complete the annual health check, as already nationally recommended, and advice on common side effects and signs of toxicity, though these are not specific to the ID population. Therefore, we propose that whilst a systematic review would provide higher quality evidence, our protocol provides a practical, timely and useful guide and aide memoire for clinical practice.

We feel the protocol well balances the need for accurate and consistent monitoring with burden on clients and the healthcare system, though opinions

on where this balance should properly sit may vary between observers. The protocol structure is reliant upon appropriate healthcare workers assessing acute changes in health and behavior of patients and conducting necessary investigations in addition to those laid out. This goes without saying as a core tenet of clinical practice, though remains vital within the provision of healthcare to people with ID.

In considering only one geographical area our pilot audit was limited by small sample size. As only one method of extracting data was used, we were reliant upon access and correct recording of test results on GP systems. Further, the audit was retrospective in nature of examining data. However, when considered purely within the confines of assessing whether all health parameters are currently being monitored, and therefore providing evidence for whether clearer protocols may improve monitoring standards, we propose that our small audit is suitable to answer this question. Next steps could be development of this project into a quality improvement initiative encompassing obtaining physician feedback on the protocol, considering if more guidance/training is needed for the additional advice, e.g., assessing acute changes.

## Conclusions

Our protocol represents the first standardized, personalized approach for monitoring lithium and associated health parameters in people with ID. The protocol captures key needs of people in this cohort as established by rapid literature review and expert discussion. This audit is possibly the first review of such health parameters within this population in a systematic way.

Application of the audit highlighted that the population examined had most essential tests within the required timeframe. Some groupings of results point toward a lack of understanding around monitoring. Our protocol should help clarify and improve this if incorporated systematically. Results may be mirrored in other service areas; further audits would reveal this and may highlight a need for centralized improvement of service in this area and therefore a national requirement for a protocol such as ours to guide clinical practice.

This audit gives proof of concept of a need for improved formalized guidance for monitoring of lithium prescribing in the community, which we believe our protocol provides. It has identified a gap in the STOMP program which has not included lithium within its ambit.

## Disclosure Statement

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## ORCID

Rohit Shankar  <http://orcid.org/0000-0002-1183-6933>

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