

Dr Sumeet Gupta<sup>1</sup>, Dr Udayan Khastgir<sup>2</sup>, Dr Ogba Onwuchekwa<sup>3</sup>, Dr Ioana Varvari<sup>4</sup>

## Monitoring the adverse effects of psychotropic drugs – need for an evidence-based approach

<sup>1</sup> Consultant Psychiatrist with Harrogate Community Mental Health Team, part of Tees, Esk and Wear Valleys NHS Foundation Trust, UK, and visiting senior lecturer at York University,

<sup>2</sup> Consultant psychiatrist with Darlington Crisis Team, part of Tees, Esk and Wear Valleys NHS Foundation Trust, UK.

<sup>3</sup> Senior Registrar working for Leeds and York Partnership NHS Foundation Trust. And general adult higher trainee pursuing an endorsement in liaison psychiatry.

<sup>4</sup> Psychiatry Registrar with Tees Esk and Wear Valleys NHS Foundation Trust.

\*email: [sumeet.gupta@nhs.net](mailto:sumeet.gupta@nhs.net)

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### Abstract

Psychotropic drugs (those that affect a person's mental state) are frequently associated with adverse effects. For many physical adverse effects, it is necessary to do baseline blood tests to avoid giving medication to patients who are at a high risk of particular adverse effects and to monitor blood tests to either avoid or manage specific adverse effects. Most treatment guidelines recommend blood tests to monitor the adverse effects of psychotropic drugs.

However, most of the recommendations from commonly used practice guidelines are based on expert opinions and low levels of scientific evidence leading to wide variations in recommendations. This area is a clinically significant area which has not received due attention from clinicians and researchers alike... In this review, we have compared blood test monitoring recommendations, by various national and international treatment guidelines, of commonly used psychotropic drugs such as antipsychotic drugs, and mood stabilising drugs. This is a narrative review, in which we have critically appraised the recommendations and highlighted the need for evidence-based monitoring of adverse effects of psychotropic drugs. Finally, we have made suggestions to make the monitoring recommendations more scientifically valid and meaningful.

### Keywords

*Psychotropic Drugs, Adverse Effects, Monitoring, Management Of Adverse Effects, Practice Guidelines*

### INTRODUCTION

All pharmacological interventions are associated with adverse effects; psychotropic medications (those that affect a person's mental state) are no exception. The choice of psychotropic for a patient is often driven by effectiveness and the adverse effects of the medication, as well as a myriad of other factors (Zimmerman et al., 2004). The adverse effects burden is one of the commonest cited reasons for non-compliance in mental health services (Agyapong et al., 2009). Therefore, the reduction of the burden of adverse effects is one of the main clinical priorities for patients and clinicians.

The adverse effects of psychotropic medications vary from mild transient to long-term serious, including fatal effects. Sometimes these adverse effects are predictable

and dose-dependent, (e.g., sedation, extrapyramidal symptoms, akathisia) but some others are unpredictable and idiosyncratic reactions (e.g., agranulocytosis, neuroleptic malignant syndrome) to medications. Therefore, the monitoring of adverse effects is important in managing them.

The summary of product characteristics (SmPC) is a legal document approved as a part of the marketing authorisation of medication by a regulator (European Medicines Agency, US Food & Drug Administration, and Medicines and Healthcare products Regulatory Agency in the UK). The SmPC contains detailed information about the medications, that include their adverse effects profile and also makes recommendations for the monitoring of significant adverse effects. It is updated regularly based on post-marketing studies or reports from clinicians

and patients. However, spontaneous reporting systems put in place by drug regulators to stimulate reporting by clinicians suffer from poor reporting, because of a lack of interest in reporting (Hazell and Shakir, 2006). Moreover, establishing causality of an adverse effect can be at times challenging and might require careful analysis of many factors (Naranjo et al., 1981). In clinical practice, patients should be informed about possible adverse effects and the monitoring requirements by the clinicians, before commencing on a psychotropic drug.

Most adverse effects can be monitored via direct reports made by patients or elicited by clinicians. The involvement of a wider team including clinical pharmacists has been shown to improve the recognition of adverse effects (Stuhec and Gorenc, 2019).

However, some adverse effects, such as drug-induced diabetes, raised cholesterol, triglyceride levels or neutrophil counts, can be prevented and recognised early on through blood tests.

It is generally accepted that all monitoring would be beneficial for patients. However, it depends on many factors and comes with many unintended consequences. For example, intense monitoring with inconvenient and frequent blood tests might dissuade patients and clinicians from using effective medication. We know this is the case with clozapine and lithium (Malhi et al., 2012; Siskind and Neilson, 2020). In a survey of patients with schizophrenia for whom clozapine was suggested, about 35% of the patients refuse to consider clozapine because of the need for monitoring and perception of the severity of its adverse effects (Gee et al., 2017). Moreover, the cost of the monitoring in mental health services is substantial and all monitoring might not be worthwhile.

Monitoring of adverse effects of psychotropic drugs is a central activity in the management of most psychiatric conditions. The SmPC of a drug include details of its adverse effects and also makes recommendations about monitoring of adverse effects. However, most of the guidelines regarding the monitoring of the adverse effects of psychotropic drugs have evolved gradually from clinical practice and are based on expert opinions. Hence, it is not uncommon to find varying recommendations from national and international guidelines. It is also surprising that most clinical guidelines, including The National Institute for Health and Care Excellence (NICE) guidelines for mental health disorders, do not justify the monitoring recommendations, regarding the choice of parameter and frequency of monitoring (2014a,b). This is largely due to a lack of scientific research assessing the utility of monitoring recommendations in mental health.

The purpose of this article is to raise the issue of a lack of scientific evidence in the monitoring of adverse effects of psychotropic drugs rather than providing recommendations. We have reviewed the monitoring recommendations of various guidelines and critically appraised the recommendations.

### *Principals of monitoring*

The main purpose of monitoring is to enable the prevention, early identification, and effective management of adverse effects. Baseline blood tests are carried out to avoid initiating said treatment in patients who are at a high risk of specific adverse effects and to ensure that changes in the monitoring parameters can be reliably attributed to treatment. After that, regular blood tests are carried out at pre-specified intervals to ensure the early identification and management of adverse effects. The recommendations for parameters, frequency and duration of monitoring should be based on the pathophysiology and clinical significance of the adverse effects. Moreover, before proposing any form of monitoring, we must be reasonably sure that such monitoring will improve clinical outcomes for patients (Glasziou et al., 2005).

The broad guidelines for monitoring adverse effects are: the adverse effects should be clinically significant and relevant; there should be a reliable test that can detect a substantial difference; early identification should improve outcomes and when identified, effective management options should be available (Glasziou et al., 2008).

We should also assess the risk of identifying false positives and unnecessary interventions thereafter.

In other words, it should be relatively clear how to interpret and react to abnormal results. We should avoid over-reacting to the random variation of parameters such as stopping lithium based on one abnormal estimated glomerular filtration rate (eGFR) value. We should also not retest until there is a real chance of change, such as measuring lipid profile (selection of blood tests used to find cholesterol and triglyceride abnormalities) a week after starting an antipsychotic drug. One should also be aware of dose-response curves for both benefits and harms. Finally, the advantages of monitoring should justify the resources used for monitoring.

The frequency of monitoring should be driven by the course and clinical significance of the adverse effects. For example, if adverse effects appear earlier in the treatment, then the monitoring should be more frequent

in the initial phase of the treatment. For example, the risk of agomelatine-associated hepatotoxicity is significantly higher in the first six months. Hence, regular blood tests for liver function tests (LFTs) have been recommended for this period only. After that LFTs should be informed by clinical condition.

There has been substantial research evidence regarding monitoring for the prevention of diabetes. Based on modelling, it has been suggested that more frequent monitoring is not always cost-effective and monitoring becomes more effective if it is linked with active intervention (Si et al., 2014; Kahn et al., 2010). Hence, the monitoring strategies should be subjected to scientific scrutiny to ensure these are beneficial to patients and are also cost-effective use of the resources. Moreover, monitoring recommendations should also emphasise interventions linked with the recommendations.

### ***Monitoring of adverse effects of lithium***

Lithium is recommended as a first-line drug for the maintenance of bipolar disorder and as an augmenting agent for treatment-resistant depression. Its most clinically significant adverse effects include weight gain, hypothyroidism, hypercalcemia, and renal adverse effects that include chronic kidney disease (CKD) and renal failure. The SmPC of lithium specifies that renal thyroid and cardiac function (especially in patients with cardiovascular disease) should be evaluated in all patients at baseline and periodically. However, it does not elucidate the parameters and frequency of monitoring. NICE guidelines for bipolar disorder (2014b) recommend the following baseline measures before initiating lithium: weight/body mass index, blood tests for urea and electrolytes including calcium, eGFR, thyroid function and full blood count (FBC). It also recommends six-monthly weights, urea and electrolytes including calcium, eGFR and thyroid function tests. Therapeutic monitoring of serum levels of lithium is also important not only in ensuring effective and safe serum levels but also in managing its dose-related adverse effects such as tremor and possibly polyuria/polydipsia or chronic kidney disease.

### ***Thyroid function tests***

NICE guidelines for bipolar disorder (2014) recommend measuring “thyroid function” at baseline and thereafter every six months. A thyroid function test usually refers to thyroid stimulating hormone (TSH) and thyroxin (T4) levels. NICE guidelines for the management of thyroid disorder (2019) recommended measuring only TSH if secondary hypothyroidism (pituitary disease)

is not suspected. Additionally, T4 is to be done only in patients whose TSH level is above the reference range. It also recommends that people with subclinical hypothyroidism have annual thyroid function tests if they have features suggestive of an underlying disease or raised thyroid autoantibodies. Otherwise, they should have thyroid function tests every two to three years.

Hypothyroidism is a common adverse effect of lithium and the reported prevalence of hypothyroidism and subclinical hypothyroidism varies from 8-19 % and 23% versus 0.5%-1.8% and 10.4% in the general population (Kleiner et al., 1999). The risk of hypothyroidism in the general population is higher in females and older/elderly people, and for patients who have raised thyroid autoantibodies. Hence, not surprisingly, lithium-associated hypothyroidism is five times more common in females and eight times more in patients with thyroid autoantibodies (Bocchetta et al., 2007). The patients are most likely to develop lithium-associated hypothyroidism within 6-18 months of the initiation, though some patients develop hypothyroidism later as well (APA bipolar guideline 2002). One cohort study reported a 2.15% risk of developing hypothyroidism/year; which is substantially less than the 5-8%/year reported risk for the conversion of subclinical hypothyroidism to overt hypothyroidism in the general population (Bocchetta et al., 2001; Karmisholt et al., 2011).

The parameters for monitoring of thyroid function in various guidelines also include baseline TSH, a full thyroid profile, thyroid antibodies and ultrasound of thyroid and follow-up monitoring recommendations also varies from six to 12 months (Table 1). A few authors have also recommended more intense monitoring in > 45-year-old females based on high risks (Kirov et al., 2005; Lazarus, 2009). One possible option could be to do more intense monitoring of high-risk patients (female and with thyroid antibodies) during high-risk periods (initial 18 months) and less intense monitoring afterwards and for low-risk patients. The SmPC also mentions that lithium should not be commenced unless a patient is euthyroid (has a normally functioning thyroid gland).

### ***Renal function***

Lithium is associated with an array of renal adverse effects (relating to the kidney function). The most common initial adverse effect is that of impaired urinary concentration (up to 40%) and this presents as polyuria and polydipsia. This can be easily picked up by educating the patients and carefully eliciting the symptoms. Other adverse effects include the long-term risks of CKD in about 20% of patients on lithium therapy, which can

progress to CKD stage 5 or end-stage renal disease (Bendz et al., 2010; Gupta et al., 2013; Raja, 2011). Lithium is primarily excreted by renal route hence patients with CKD are at a high risk of renal toxicity and more likely to progress to end-stage renal disease. Hence, lithium should be used very cautiously in this population and it is contraindicated in patients with severe CKD.

CKD, on the other hand, does not initially present with any signs or symptoms. Hence, regular blood tests are needed to identify glomerular impairment. Apart from the risk of progression, CKD is also associated with an increased risk of cardiovascular disorders (Gupta et al., 2013).

NICE guidelines for bipolar disorder (2014b) recommends baseline urea, electrolyte and eGFR tests, then repeating these tests at six-monthly intervals. Additionally, if urea and creatinine levels become elevated or eGFR consecutively reduces over two more tests then we need to assess the rate of deterioration of

the renal function and to follow NICE guidelines on CKD.

Lithium-associated CKD is usually insidious in onset and becomes apparent only after many years of Lithium therapy. NICE's CKD guidelines (2014c) recommends more than once in a year monitoring of renal function only if eGFR decreases less than 45ml/min or if a decline in eGFR is associated with significant proteinuria; even in patients suffering from a systemic disease which is affecting the renal function (such as diabetes and hypertension) or taking the nephrotoxic drug (such as non-steroidal anti-inflammatory drugs). Hence, the six-monthly monitoring of renal function in all patients is not proportional to the risks. Moreover, there is a dearth of guidance around the best ways to deal with the abnormal results and there is still doubt about whether these are reversible or irreversible adverse effects. However, there is largely a consensus that in most cases risks and benefits analysis will favour the continuation of lithium (Gupta et al., 2013; Werneke et al., 2012).

**Table 1:** Recommendations of diverse guidelines on routine monitoring of patients treated with lithium.

	Recommended baseline tests	Recommended follow-up monitoring	Comments
British National Formulary (2020).	Renal and thyroid function and electrolyte (including calcium).	Serum electrolyte (including calcium), eGFR and thyroid function every six months.	More frequent blood tests if there is any evidence of impaired renal and thyroid function or raised calcium levels.
National Institute of Health and Care Excellence (2014).	Urea and electrolyte (including calcium) eGFR and thyroid function.	Urea and electrolyte (including calcium) eGFR and thyroid function every six months.	In case of deterioration of renal function (raised urea and creatinine levels or if eGFR falls for two or more tests then assess the rate of deterioration of renal function. In the latter case for NICE guidelines for CKD and acute kidney injury).
British Association for Psychopharmacology (2016).	Blood creatinine concentrations + e-GFR Thyroid function	Renal and thyroid function – every 12 months patients with stable thyroid and renal function and no lithium dose change or whenever clinical status change.	
International Society for Bipolar Disorder (2018).	Electrolytes including calcium Serum creatinine e GFR 24-hour creatinine clearance (if history of renal disease) TSH	Thyroid + renal + calcium at six months and at least annually thereafter or as clinically indicated.	In older and elderly patients (> 66 year of age) eGFR should be measured at least every three to six months.
American Psychiatric Association (2002).	Urea and creatine level measurement and thyroid Function	Renal function should be tested every two to three months during the first six months. Thyroid function should be evaluated once or twice during the first six months. After that renal and thyroid function may be checked every six months to one year in stable patients or whenever clinically indicated.	
Royal Australian and New Zealand College of Psychiatrists (2015).	Renal (urea, creatinine, electrolytes) Endocrine (TSH, Serum calcium, parathyroid hormone)	All baseline parameters to be repeated after six months of the initiation then annually.	
SmPC (2020).	Renal and thyroid function Cardiac function in patients with cardio-vascular disease	Renal, cardiac and thyroid function should be reassessed periodically.	It does not specify tests to assess thyroid or renal function.

eGFR- estimated glomerular filtration rate, TSH-Thyroid stimulating hormone.

Like NICE guidelines, other guidelines also continue to suggest monitor renal function by monitoring urea, creatinine apart from eGFR.

Measuring urea levels is no longer recommended for the monitoring of the renal function. eGFR is preferred over urea and creatinine levels, as urea level is also affected by many non-renal factors. On the other hand, the recommended frequency of monitoring varies from three to 12 months (Table 1).

Moreover, renal function gradually decreases with age; it is a normal part of the ageing process and can also be affected by non-renal factors. Hence, measuring eGFR frequently is likely to lead to false alarms and many patients might suffer more harm from the discontinuation of lithium. Recent literature, including the NICE CKD guidelines (2014c), has suggested that urine albumin creatinine ratio (ACR) along with eGFR should be used to monitor renal function, as these two parameters complement each other in predicting the risk of a further worsening of renal function. Recently psychiatric guidelines also started to add ACR to monitor the renal function in established cases of CKD (Gupta et al., 2013; Kripalani et al., 2009).

Therefore, it would be useful if the recommendation regarding monitoring of renal function can be revised both in terms of parameters and frequency. Current recommendations of NICE guidelines of six-monthly monitoring appear to be excessive considering the risk and course of the adverse effects. Moreover, it does give the impression that lithium is more nephrotoxic (damaging to the kidneys) than diabetes or hypertension. It would also be helpful to produce specific guidance regarding the management of lithium associated renal impairment. Annual or less frequent monitoring of renal function using eGFR might be a more efficient way of monitoring and if a patient presents with the rapid decline of renal function or suffers from CKD, then monitoring should become more frequent and should also include ACR (APA, 2002; BAP, 2016; Gupta et al., 2013; Kripalani et al., 2009)

### ***Hypercalcemia***

Lithium can occasionally cause hypercalcemia, reportedly a wide range of prevalence 3.2 -62% (Kuman Tunçel et al., 2019); the wide range is due to a limited number of small studies in this area.

A systematic review and meta-analysis about the adverse effects of lithium found that blood calcium and

parathyroid hormone levels were up to 10% higher in patients on lithium compared with controls (McKnight et al., 2012). The patients with mildly raised calcium levels might not present with any symptoms and only require careful monitoring. On the other hand, significant high levels or symptomatic hypercalcemia (presenting with mood symptoms, renal stones or osteoporosis) will require either treatment with cinacalcet or surgical intervention (Gitlin, 2016). This is usually a long-term adverse effect, although cases have been reported within one to two months of initiation of lithium (Szalat et al., 2009).

Most guidelines recommend monitoring calcium levels (Table 1). The Royal Australian and New Zealand College of Psychiatrists (2015) also recommends measuring the parathyroid hormone. On the other hand, recent NICE guidelines have altered the previous recommendation of annual monitoring every six months. It has not elaborated on the reason for the change. We assume that might be because they have recommended six-monthly monitoring of other parameters. The SmPC mentions parathyroid adenoma and hyperparathyroidism as adverse effects, but does not recommend any monitoring for these adverse effects.

This is an under-researched area and in clinical practice, we very infrequently come across patients who require discontinuation of lithium or medical or surgical intervention to manage hypercalcaemia. At present, based on the available evidence, it would be prudent to monitor calcium levels at least annually for all patients and more frequent estimation of calcium and parathyroid hormones in patients with hypercalcemia. However, it is an under-researched area and in clinical practice and more research is required to establish the utility of frequency of calcium monitoring.

### ***Monitoring of adverse effects of antipsychotic medications***

Antipsychotic drugs are associated with a variety of neurological, endocrinal and metabolic adverse effects (Huhn et al., 2019). NICE guidelines for schizophrenia and bipolar disorders recommend the following baseline parameters; weight, waist circumference, pulse, blood pressure, assessments for any movement disorders, and laboratory tests (fasting blood glucose, HbA1C, lipid profile and prolactin levels). The monitoring of weight is recommended every week for the first six weeks, following which all measures except prolactin should be done at three months and 12 months thereafter annually. The SmPCs of antipsychotic drugs' recommendations varies significantly. Generally, these recommend



monitoring of weight, blood sugar and lipid profile of antipsychotic drugs that are likely to have these adverse effects such as olanzapine and quetiapine etc, but these do not specify the frequency of monitoring or make any management recommendations.

The main purpose of the monitoring is to prevent and manage weight gain and reduce the risk of developing diabetes and hyperlipidaemia, to reduce morbidity and mortality due to cardiovascular disorders.

NICE guidelines for schizophrenia and bipolar disorders (2014a,b) suggest carrying out both fasting blood glucose and HbA1C levels at baseline and the specified intervals. However, recent NICE guidelines (2015) regarding the management of diabetes prefer HbA1c over fasting glucose level for the screening of patients for diabetes. Recently one retrospective study compared monitoring received by diabetic patients with or without severe mental illness, but they did not find any difference between monitoring received by the two groups. However, they did find higher mortality and less planned interventions in the severe mental illness group. One of the possible explanations is a lack of early diagnosis of complications and interventions in severe mental illness groups (Han et al., 2021).

This study highlights that apart from improving compliance with the monitoring we need to link appropriate interventions with the monitoring. Similarly, as we know that the treatment for hyperlipidaemia is guided by the risk of cardiovascular disorders; assessed by Q-risk factors or similar risks scores. Hence, it would be useful if the guidelines specify the management of these risk factors. Development of the Lester tool and Q-risk 3 (which takes into account the risks due to severe mental illnesses and atypical antipsychotics) are useful developments and should be incorporated into the relevant guidelines (Shiers et al., 2014; Hippisley-Cox et al., 2017).

Antipsychotic-induced hyperprolactinaemia (high prolactin levels) is an important adverse effect; however, NICE guidelines for schizophrenia and bipolar disorder (2014a,b) provide no information about repeating prolactin level or managing it. Hyperprolactinaemia is commonly seen with antipsychotic drugs like risperidone, paliperidone, amisulpride or typical antipsychotic drugs. The SmPCs of the above drugs does mention raised prolactin as an adverse effect, but do not recommend any monitoring. Similarly, there is a wide divergence of recommendations, with regards to parameters and frequency among different guidelines (Table 2). The relationship between the degree of hyperprolactinaemia

and symptoms is variable. We can have patients with very high levels of prolactin but without any symptoms and vice versa. Patients with high prolactin levels commonly present with sexual or menstrual problems. Due to the nature of symptoms, patients voluntarily do not disclose sexual problems and are more likely to discontinue the treatment (Montejo et al., 2010). Moreover, even asymptomatic patients can suffer from long-term adverse effects such as infertility and osteoporosis. Therefore, it has been recommended that all patients on antipsychotic drugs should have a baseline and after three months of the initiation of an antipsychotic drug, serum prolactin levels check (Gupta et al., 2017). Investigating those cases in which a patient presents with the symptoms is likely to result in many patients with clinically significant hyperprolactinaemia being missed.

Clozapine is the drug of choice for treatment-resistant schizophrenia. However, there have been concerns regarding the underutilisation of clozapine and many patients have to wait and undergo trials of several antipsychotic drugs lasting a few years before initiation of clozapine (Rubio, 2020). One of the main reasons is a strict protocol regarding the need for regular blood tests to ensure early detection of potentially fatal agranulocytosis. Clozapine was withdrawn in 1975 after the death of patients on clozapine due to agranulocytosis in Finland. In 1989 it was reintroduced in many countries with strict protocols, and drug manufacturers were given the responsibility to ensure its safe use. Current recommendations in most European countries, including the UK, state that the white blood cell count must be checked prior to the commencement of clozapine, and then monitored as follows: weekly for the first 18 weeks then fortnightly until week 52 and afterwards four-weekly monitoring.

Over the years, it has become clear that clozapine associated agranulocytosis is not as common as once it was believed. Current literature suggests the risk of developing agranulocytosis is about 0.7% and the majority of the cases of agranulocytosis have been reported within the first year of the initiation. The risk after a year decreases drastically to about 0.07%, which is not very different from other antipsychotic drugs (Schulte 2006; Verbelen et al., 2015; Myles et al., 2018). Additionally, with the advent of newer treatments most patients with agranulocytosis can be treated and its fatality rate is about 3%. The chances of a patient on clozapine dying due to complications related to agranulocytosis is estimated to be 0.016 %, which is significantly less than the risk of someone dying in Europe due to a road accident (Ingimarsson et al., 2016).

**Table 2:** Recommendations of diverse guidelines on routine monitoring of patients treated with antipsychotic drugs

	<b>Recommended baseline tests</b>	<b>Recommended follow-up monitoring</b>	<b>Comments</b>
British National Formulary (2020).	FBC, Renal and Liver function  FBG/ Hba1c  Lipid profile	Annually  At four to six months and thereafter annually  At three months and thereafter annually	
National Institute of Health and Care Excellence (2014).	Blood Sugar, FBG, HBA1c Lipid Profile  Prolactin levels	At 12 weeks and then annually.  Does not specify	
<i>Maudsley</i> Guidelines (2018).	Renal (U&E's + eGFR) FBC  Blood lipids  FBG  Prolactin LFTs	Annually as part of the routine check at three months and then annually thereafter  At four to six months and then annually thereafter  At six months and then annually thereafter Annually	They recommend HbA1C only if FBG is abnormal.
American Psychiatric Association (2020).	FBC  Renal, liver, thyroid function and electrolytes  Fasting blood glucose or HbA1c, lipid profile  Screen for metabolic syndrome criteria  Prolactin if indicated on clinical history	Every visit for six months and at least quarterly thereafter  If clinically indicated (Clozapine)  At four months and at least annually thereafter  At four months and at least annually thereafter  Screening for symptoms of hyperprolactinemia at each visit until stable, then yearly if treated with an antipsychotic known to increase prolactin.	
World Federation of Societies of Biological Psychiatry (2013).	Fasting plasma glucose and Fasting Lipid profile FBC	At 12 weeks and annually thereafter;  At four and 12 weeks and annually thereafter.	
Royal Australian and New Zealand College of Psychiatrists (2016).	FBG, HbA1c and Fasting lipid profile  Prolactin and FBC	At 12, 24 weeks and annually thereafter  At 24 weeks and annually thereafter	Prolactin can be more frequently monitored if clinically indicated.

eGFR – estimated glomerular filtration rate, FBC – full blood count, FBG – fasting blood sugar, Hb1Ac – glycated hemoglobin, LFT– liver function tests, U&E – urea and electrolytes

Table 3: Recommendations of diverse guidelines on routine monitoring of patients treated with valproate.

	Recommended baseline tests	Recommended monitoring	follow-up	Comments
British National Formulary (2020).	LFT FBC			A more frequent monitoring is recommended in the first 6 months if patients are more at risk.
National Institute of Health and Care Excellence (2014).	FBC LFT	At six months and yearly thereafter		
British Association for Psychopharmacology (2016).	LFT	First six months		They emphasise on clinical vigilance being more important than the measurements.
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) Guidelines (2013).	FBC Fasting glucose Fasting lipid profile Platelets Electrolytes and calcium LFT Prothrombin and partial thromboplastin time U&E's + e GFR Prolactin	Hematology profile and LFTs should be obtained at three to six month intervals during the first year, and yearly thereafter and as clinically indicated.		
Maudsley Guidelines (2018).	Same as NICE and BAP	Same as NICE and BAP		The only difference is that they mention SPC recommendations: More frequent LFTs in the first months and albumin and clotting panel.
American Psychiatric Association (2002).	LFTs  FBC	LFT and hematological investigations Every six months		
Royal Australian and New Zealand College of Psychiatrists (2015).	FBC LFTs	At six, 12 and 24 months		They mention that the risk of severe liver damage is greatest in the first months of therapy.
SmPC (2021).	LFT FBC	Periodically during the first three months, in high-risk patients.		Among usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

FBC – full blood count, LFTs – liver function tests.

Therefore, over the past few years, questions have been raised about both frequency of blood monitoring and cut off criteria. US FDA has already changed the monitoring criteria and introduced more flexible stoppage rules. According to the new recommendations clozapine therapy should be interrupted for an absolute neutrophil count (ANC) is less than  $1/10^9/L$ , if the prescriber suspects clozapine-induced neutropenia. Even when the ANC drops below  $1/10^9/L$ , the prescribers can continue to prescribe clozapine if they consider the benefits to outweigh risks for a given patient (Oloyede et al., 2021). Now there is a growing call to make blood monitoring less frequent, after a year to less frequent or discontinuing it completely and also to change the recommended actions based on the blood results (Ingimarsson et al., 2016; Shulte, 2006; Myles et

al., 2018). No doubt that the strict monitoring protocols have saved many lives, but it might have also deprived many patients of a most effective treatment for their illness. Moreover, the benefits of clozapine including reduced all-cause mortality should also be taken into account.

**Monitoring of adverse effects of valproate**

Valproate has been used as a mood stabiliser for many years. Its common adverse effects include weight gain, tremor, sedation, liver toxicity and haematological alterations such as thrombocytopenia and leucopenia. The hepatic and haematological adverse effects could be fatal, hence monitoring is usually recommended for LFTs and haematological parameters (Murru et al.,



2015). The SmPC of valproate recommends that liver function should be measured before therapy and then periodically monitored during the first six months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Among usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. NICE guidelines for bipolar disorders (2014b) suggest baseline weight, LFTs and FBC checks. It provides a further explanation regarding LFTs and states that there is a poor correlation between absolute values of hepatic enzymes and the extent of liver damage and states that the accepted norm of the clinical significance of raised LFTs is persistent elevation of liver enzymes more than three times of the upper normal limit (ULN). Furthermore, raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease. The latter is also suggested in the SmPC. For follow-up monitoring, the guidelines recommend repeating weight, LFTs and FBC, six months following the initiation and then repeating these tests annually. Table 3 illustrates the recommendations of the SmPC and various guidelines.

Valproate is known to be associated with a variety of hepatic adverse effects, these vary from common asymptomatic elevation of liver enzymes to severe liver toxicities (acute hepatocellular injury and hyperammonia). The mechanism through which valproate can cause hepatic injury and failure is not yet fully understood. For clarity, it is perhaps important for our reader to understand that there are two types of drug-induced liver injuries (DILI). The first one is intrinsic, which is expected, dosage-related, often asymptomatic, with onset at initiation and recovers with dose adjustment. The cut off for identifying the clinically significant DILI is a raise in alanine aminotransferase (ALT) and aspartate transaminase (AST) > 3xUNL. This arbitrary cut off appears to separate intrinsic DILI (with the potential of evolving in acute hepatic injury if not acted upon) from a normal, again expected, adaptive reaction of the liver metabolising a new chemical component which usually is self-remitting. 10-20% of patients on valproate therapy are reported to have a transient rise of liver enzymes. The available evidence so far states that this reaction and its development is expected to appear with treatment initiation to the six months, being uncommon thereafter, depending on dosage increase, therapeutic ranges and developing comorbidities (Telles-Correia et al., 2017).

The second one is called idiosyncratic reaction and is more specific for valproate induced acute hepatocellular

toxicity. This reaction is unexpected and can develop between two days and three years from initiation of medication, mostly within the first six months of the initiation for valproate (Schmidt & Siemes, 1998; Telles-Correia et al., 2017).

It affects 1 in 20,000 to 49,000 patients receiving the medication. Young age (<2 years), presence of other neurological conditions and concurrent use of other anticonvulsants appear to be important risk factors for acute hepatocellular toxicity, and this is rare in adults. Most patients present with sudden onset jaundice, lethargy, nausea, vomiting, and abdominal pain and more often these symptoms precede the elevation of liver enzymes. Hence, it has been suggested that regular yearly monitoring is unlikely to screen for the above adverse effect. The only reliable factors appear to be a clinical presentation and educating the patients about the early warning signs and symptoms. EASL Clinical Practice Guidelines describe different patterns of idiosyncratic liver injury (hepatocellular – ALT > 5x upper limit of normal value (ULN); cholestatic – alkaline phosphatase (ALP) alone >2x ULN; and mixed with an ALP/ALT ratio between 2 – 5). These cases warrant discontinuation of valproate and urgent medical attention. The guidelines suggest the importance of regular monitoring of LFTs to effectively manage DILI, as in most cases it will include either reducing the dose or stopping the medication, once there is reasonable doubt about the causality. They also suggest regular monitoring of LFTs but also stressed that the frequency of monitoring interval should be informed by the level of evidence for a DILI hazard attributable to the drug. They also suggest using big data to estimate the risk of adverse hepatic reactions from individual drugs (EASL, 2019).

There is some evidence and pertinent biological theories that support and describe the importance of monitoring the LFTs in the first six months. There is little to support and encourage the monitoring after this period, the evidence becoming scarce after one to two years and almost non-existent after three years. Annual routine investigations are unlikely to catch this in the absence of clinical symptomatology. Moreover, after this period of time, other factors should also be considered such as patient's comfort (a constant reminder of disease), costs and compliance with treatment (Meijboom & Grootens, 2017; Schmidt & Siemes, 1998). BAP Guidelines and Meijboom and Grootens, 2017, advise abandoning regular monitoring of LFTs and suggest that monitoring can be effectively done by careful monitoring of symptoms. However, there are still lots of uncertainties about the risk of long-term clinically significant hepatic

adverse reactions associated with valproate and the utility of regular monitoring of LFTs.

Valproate has also been implicated in haematological abnormalities such as thrombocytopenia, neutropenia, leucopenia and pancytopenia. The reported prevalence of thrombocytopenia ranges from 0.6-27.8 %. The risk is more significant in the first year after initiation. On the other hand, the risk of neutropenia and leucopenia is more in the first two years. The reported prevalence of the two conditions is 26% and 0.4%. Most of these adverse effects can be managed by reducing the dose of valproate. As blood tests can pick up abnormality before the emergence of symptoms, hence regularly checking FBC in the first two years, after every three to six months, following initiation of valproate or after the change of dose has been recommended (Meijboom & Grootens, 2017). The risk is very minimal after two years. Hence, there is very limited utility in continued monitoring after two years.

## CONCLUSION

Adverse effects of psychotropic drugs should be identified and managed proactively by clinicians, and they should have a detailed discussion with patients about possible adverse effects before the initiation of psychotropic drugs. The monitoring of adverse effects of psychotropic drugs is an essential component in the management of most severe psychiatric disorders. Unfortunately, monitoring guidelines including NICE guidelines have not received the due scientific scrutiny and attention and, so, most of the recommended monitoring in the NICE guidelines are based on lower levels of scientific evidence.

The argument can be made for more frequent monitoring of any adverse effects as the assumption is that it will always be beneficial. However, this may not be the case. Frequent monitoring might result in decreased use of effective medication. Or, worse still, unclear guidelines might also lead to the inappropriate discontinuation of an effective treatment.

We propose that in the future the guidelines making monitoring recommendations should give rationales justifying the recommendations like they do for any treatment recommendations. Additionally, monitoring recommendations should also be accompanied by expected interventions based on abnormal results. We hope that this would reduce the divergence of recommendations and allow readers to critically appraise the recommendations. It would also be

worthwhile to compare the effectiveness of different monitoring recommendations, not only in terms of beneficial effects to patients (such early identification and effective management of adverse effects) but also in terms of cost-effectiveness as well. This can be achieved by conducting prospective cohort studies or randomised controlled trials. Lastly, all monitoring recommendations should be updated regularly based on the most recent available data, following the principles of evidence-based medicine.

## DECLARATIONS

We confirm that all authors have read and understood the conditions of publication of this paper in the journal. We also confirm that the paper has been solely submitted to this journal and is not published or under review in any other journal.

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## REFERENCES

- Agyapong VI, Nwankwo V, Bangaru R, Kirrane R. Sources of patients' knowledge of the adverse effects of psychotropic medication and the perceived influence of adverse effects on compliance among service users attending community mental health services. *J Clin Psychopharmacol.* 2009 Dec;29(6):565-70.
- American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry.* 2002 Apr;159(4 Suppl):1-50.
- Bendz H, Schön S, Attman PO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney Int.* 2010 Feb;77(3):219-24.
- Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A. Fifteen-year follow-up of thyroid function in lithium patients. *J*

- Endocrinol Invest. 2007 May;30(5):363-6.
- Bocchetta A, Mossa P, Velluzzi F, Mariotti S, Zompo MD, Loviselli A. Ten-year follow-up of thyroid function in lithium patients. *J Clin Psychopharmacol*. 2001 Dec;21(6):594-8.
- European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu Clinical Practice Guideline Panel: Chair: Panel members et al. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol*. 2019 March;70:1222-61.
- Gee SH, Shergill SS, Taylor DM. Patient attitudes to clozapine initiation. *Int Clin Psychopharmacol*. 2017 Nov;32(6):337-342.
- Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord*. 2016 Dec;4(1):27.
- Glasziou P, Irwing L, & Aronson J (2008). Evidence-based Medical Monitoring: From Principles to Practice. Blackwell Publishing, Oxford, UK.
- Glasziou P, Irwing L, Mant D. Monitoring in chronic disease: a rational approach. *BMJ*. 2005 Mar 19;330(7492):644-8.
- Gupta S, Kripalani M, Khastgir U, Reilly J. Management of the renal adverse effects of lithium. *Advances in Psychiatric Treatment*. *Adv Psychiatr Treat*. 2013 ;19(6) : 457-466.
- Gupta, S., Lakshmanan D A M, Khastgir U, Nair R. (2017). Management of antipsychotic-induced hyperprolactinaemia. *BJPsych Advances*. 2017;23(4), 278-286.
- Han L, Doran T, Holt RIG, Hewitt C, Jacobs R, Prady SL, Alderson SL, Shiers D, Wang HL, Bellass S, Gilbody S, Kitchen CEW, Lister J, Taylor J, Siddiqi N. Impact of severe mental illness on healthcare use and health outcomes for people with type 2 diabetes: a longitudinal observational study in England. *Br J Gen Pract*. 2021 Jul 29;71(709):e565-e573.
- Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2006;29(5):385-96.
- Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017 May 23;357:j2099.
- Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Bäckers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019 Sep 14;394(10202):939-951.
- Ingimarsson O, MacCabe JH, Haraldsson M, Jónsdóttir H, Sigurdsson E. Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland. *BMC Psychiatry*. 2016 Dec 12;16(1):441.
- Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <<http://www.medicinescomplete.com>> [Accessed on 21 Nov 2021].
- Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, Gregg E, Holman RR, Kirkman MS, Stern M, Tuomilehto J, Wareham NJ. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet*. 2010 Apr 17;375(9723):1365-74.
- Karmisholt J, Andersen S, Laurberg P. Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy. *Eur J Endocrinol*. 2011 Mar;164(3):317-23.
- Kirov G, Tredget J, John R, Owen MJ, Lazarus JH. A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. *J Affect Disord*. 2005 Aug;87(2-3):313-7
- Kleiner J, Altschuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *J Clin Psychiatry*. 1999 Apr;60(4):249-55.
- Kripalani M, Shawcross J, Reilly J, Main J. Lithium and chronic kidney disease. *BMJ*. 2009 Jul 3;339:b2452.
- Kuman Tunçel Ö, Akdeniz F, Özbek SS, Kavukçu G, Ünal Kocabaş G. Lityumün Kalsiyum ve Parathormon Düzeyi Üzerine Etkisi: Sağlıklı Kontrollerle Karşılaştırmalı Kesitsel Bir Çalışma [The Effects of Lithium on Calcium and Parathormone Levels: A Cross-sectional Study with Healthy Controls]. *Türk Psikiyatri Derg*. 2019 Fall;30(3):163-171.
- Lazarus JH. Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab*. 2009 Dec;23(6):723-33.
- Malhi GS, Tanious M, Das P, Berk M. The science and practice of lithium therapy. *Aust N Z J Psychiatry*. 2012 Mar;46(3):192-211.
- McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012 Feb 25;379(9817):721-8.
- Meijboom RW, Grootens KP. Dispensability of Annual Laboratory Follow-Up After More than 2 Years of Valproic Acid Use: A Systematic Review. *CNS Drugs*. 2017 Nov;31(11):939-957.
- Montejo AL, Majadas S, Rico-Villademoros F, Llorca G, De La Gándara J, Franco M, Martín-Carrasco M, Aguera L, Prieto N; Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction.

- Frequency of sexual dysfunction in patients with a psychotic disorder receiving antipsychotics. *J Sex Med.* 2010 Oct;7(10):3404-13.
- Murru A, Popovic D, Pacchiarotti I, Hidalgo D, León-Caballero J, Vieta E (2015). Management of Adverse Effects of Mood Stabilizers. *Current Psychiatry Reports*, 17(8), 66.
- Myles N, Myles H, Xia S, Large M, Kisely S, Galletly C, Bird R, Siskind D. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand.* 2018 Aug;138(2):101-109.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981 Aug;30(2):239-45.
- National Institute for Health and Care Excellence (2014a) Bipolar Disorder: Assessment and Management (Clinical Guideline CG185). NICE
- National Institute for Health and Care Excellence (2014b) Psychosis and Schizophrenia in Adults: Prevention and Management (Clinical Guideline CG178). NICE.
- National Institute for Health and Clinical Excellence. (2014c) Chronic kidney disease in adults: assessment and management (Clinical Guideline CG182). NICE
- National Institute for Health and Care Excellence (2019) Thyroid disease: assessment and management (NG 145). NICE
- National Collaborating Centre for Chronic Conditions (2015). Type 2 diabetes in adults: management (Clinical Guideline 28). NICE
- Oloyede E, Casetta C, Dzahini O, Segev A, Gaughran F, Shergill S, Mijovic A, Helthuis M, Whiskey E, MacCabe JH, Taylor D. There Is Life After the UK Clozapine Central Non-Rechallenge Database. *Schizophr Bull.* 2021 Jul 8;47(4):1088-1098.
- Raja M. Lithium and kidney, 60 years later. *Curr Drug Saf.* 2011 Nov 1;6(5):291-303.
- Rubio JM, Kane JM. How and when to use clozapine. *Acta Psychiatr Scand.* 2020 Mar;141(3):178-189
- Schmidt D, Siemes H. Role of liver function tests in monitoring anticonvulsant use. *CNS Drugs.* 1998;10 (5): 321–328.
- Schulte P. Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. *Ann Pharmacother.* 2006 Apr;40(4):683-8.
- Shiers DE, Rafi I, Cooper SJ, Holt RIG. (2014) Positive Cardiometabolic Health Resource: an intervention framework for patients with psychosis and schizophrenia. Royal College of Psychiatrists, London.
- Si S, Moss JR, Sullivan TR, Newton SS, Stocks NP. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. *Br J Gen Pract.* 2014 Jan;64(618):e47-53.
- Siskind D, Nielsen J. Clozapine: a fine balance. *Acta Psychiatr Scand.* 2020 Mar;141(3):175-177.
- Stuhec M, Gorenc K . Positive impact of clinical pharmacist interventions on antipsychotic use in patients on excessive polypharmacy evidenced in a retrospective cohort study. *Global Psychiatry.* 2019; 2: 155–164.
- Summary Product Characteristics – Lithium Carbonate (2020) – <https://www.medicines.org.uk/emc/product/10829/smpc>
- Summary Product Characteristics – Olanzapine (2021) – <https://www.medicines.org.uk/emc/product/6082/smpc>.
- Summary Product Characteristics - Quetiapine (2019) – <https://www.medicines.org.uk/emc/product/8252/smpc>
- Summary Product Characteristics – Amispiride (2021) – <https://www.medicines.org.uk/emc/product/548/smpc>
- Summary Product Characteristics – Risperidone (2020) – <https://www.medicines.org.uk/emc/product/5990/smpc>
- Summary Product Characteristics – Paliperidone (2020) – <https://www.medicines.org.uk/emc/product/7652/smpc>
- Summary Product Characteristics – Valproate (2021) – <https://www.medicines.org.uk/emc/product/1446/smpc>
- Szalat A, Mazeh H, Freund HR. Lithium-associated hyperparathyroidism: report of four cases and review of the literature. *Eur J Endocrinol.* 2009 Feb;160(2):317-23.
- Telles-Correia D, Barbosa A, Cortez-Pinto H, Campos C, Rocha NB, Machado S. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther.* 2017 Feb 6;8(1):26-38.
- Verbelen M, Collier DA, Cohen D, MacCabe JH, Lewis CM. Establishing the characteristics of an effective pharmacogenetic test for clozapine-induced agranulocytosis. *Pharmacogenomics J.* 2015 Oct;15(5):461-6.
- Werneke U, Ott M, Renberg ES, Taylor D, Stegmayr B. A decision analysis of long-term lithium treatment and the risk of renal failure. *Acta Psychiatr Scand.* 2012 Sep;126(3):186-97.

Zimmerman M, Posternak M, Friedman M, Attiullah N, Baymiller S, Boland R, Berlowitz S, Rahman S, Uy K, Singer S. Which factors influence psychiatrists' selection of antidepressants? *Am J Psychiatry*. 2004 Jul;161(7):1285-9.