**Practice Pointer**

Laboratory and Physical health monitoring of Drug Interventions in People with Bipolar Disorder

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**How this article was created**

We reviewed UK (British National Formulary, National Institute for Health and Care Excellence, Royal College of Psychiatrists, Maudsley Prescribing Guidelines, British Association of Psychopharmacology) and international (European Psychiatry Association, Canadian Network for Mood and Anxiety Treatments, and International Society for Bipolar Disorders, American Psychiatric Association) guidance, and searched the bipolar disorder literature (PubMed) using terms based on drug classes and individual drug names, together with terms such as “Monitoring”, “Blood Test Monitoring”, “adverse events”, “COVID-19” and “SARS”-CoV-2”.

 We drew upon the authors’ expertise and experience in developing the quality improvement toolkit and in assessing practical considerations.

**Contributorship and the guarantor**

AAF conceived the article and is the guarantor. AAF provided a clinical laboratory perspective, RB provided clinical psychiatry expertise and was the contact for patient involvement, AHH provided an overview from both a metabolic and mental health perspective, and SZ performed detailed review of the existing guidelines. All authors wrote and reviewed the article, created the boxes, and helped with the figures and tables. The authors wish to thank the person with lived experience of bipolar disorder, who wished to remain anonymous, for contributing and agreeing the final version of their personal story.

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None

**How patients were involved in the creation of this article**

The article was reviewed by a person with bipolar disorder. They provided the patient perspective included above and also commented on the remainder of the manuscript. In response to these comments, changes were made in relation to common co-morbidities in bipolar disorder, the potential impact of antidepressant medications in some patients and the importance of streamlining the communication between general practice and specialist mental health services to minimise duplication (which was also included in our ‘tips for improving monitoring’ box; Table 2).

**Conflicts of Interest**

Competing Interest: None declared.

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Laboratory and Physical health monitoring of Drug Interventions in People with Bipolar Disorder

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| **Patient perspective: My experience of bipolar and routine health monitoring**Aged 33, I was prescribed antidepressants by my GP because of work-related stress. Five weeks later, I was diagnosed as having bipolar following manic and depressive episodes thought to be triggered by the antidepressants. For 6 years, I was managed with a combination of quetiapine and lamotrigine. However, I was admitted to hospital for 9 weeks following a manic psychotic episode and changed to valproate.In order to remain well, I ensure that I have 7 hours sleep a night and never go out the evening before work, as this keeps me awake. I don’t drink alcohol or smoke, and my Christian faith has been vital in helping me deal with bipolar.Since being on medication, I have had annual blood tests and completed the Valproate Risk Acknowledgment form, which has been carried out by both the GP surgery and the mental health team. In recent years I have also had my blood pressure, weight and general lifestyle checked – again, by both the GP surgery and the mental health team. As some of the tests are carried out separately, it results in 6 separate appointments annually for monitoring alone.As a part time nurse, I often have to rearrange my work schedule for these duplicated appointments. Ideally, I think the tests should be completed by one healthcare team and the information shared between them. |

**Introduction**

The dramatic decline in blood testing and face-to-face clinical reviews during the COVID-19 pandemic focused minds as to whether much of the long-term monitoring, previously core to the management of many long-term conditions, is needed.1,2

Bipolar disorder, represents one such condition where regular clinical interaction and monitoring of side-effects of medications is particularly important. Type 1 bipolar disorder alone affects ~1% of the population (~45 million people worldwide); around 2.5% for all bipolar spectrum disorders, though some studies suggest this may be as high as 5%.3 Often affecting a younger population, bipolar disorder is associated with significantly reduced life expectancy due to complex factors including common co-morbidities.4  A key aspect of the long-term treatment of bipolar disorder is pharmaceutical intervention, alongside individual or family psychological interventions. Pharmacological interventions require careful monitoring after initiation; this can be done either in primary or in secondary care as per the local shared care agreement.

This article aims to: (i) present a concise, accessible summary of monitoring requirements, focusing on aiding general practitioners who are increasingly responsible for prescribing bipolar disorder medications, (ii) support practitioners to improve monitoring and, (iii) suggest how checks might be safely prioritised in pandemic-like or resource-poor scenarios.

While treatment of bipolar disorder involves a range of different classes of pharmacological agents, the UK NHS recommend annual health checks for people with bipolar disorder which include both physical and laboratory assessment.5 It is therefore logical that monitoring of the different agents used should be considered together. …

**What medications requiring monitoring are commonly prescribed in general practice?**

Pharmacological treatment for bipolar disorder includes use of mood stabilisers e.g. lithium, valproate, carbamazepine, lamotrigine; antipsychotics, and antidepressants, either alone or in combination (Box 1). The usual combination of medications during mania episode would be of a mood stabiliser with an antipsychotic agent and/or short-term use of benzodiazepines (in acute presentation). For long-term management, the goal will be to prescribe minimal effective dosages. Antidepressants are still widely used in bipolar depression, particularly for breakthrough episodes occurring in those on mood stabilisers. They have been assumed to be effective, although there is a risk of cycle acceleration and/or switching.

Globally, general practitioners and practice nurses are either directly involved in caring for such patients or come into contact with them on a regular basis.

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| **Box 1: Principal pharmaceutical agents used in the treatment of bipolar disorder** |
| **Antipsychotics** | **Mood stabilisers** | **Antidepressants\*** |
| **Anticonvulsants** | **Other** |
| Second generation antipsychotics (SGA)Olanzapine\*\*Risperidone\*\* Paliperidone\*\*QuetiapineAsenapineAripiprazole\*\* CariprazineLurasidoneAmisulpride\*\*\*Clozapine\*\*\*\*First Generation Antipsychotics (FGA)Haloperidol\*\*Flupentixol\*\* Zuclopenthixol\*\*ChlorpromazineSulpiride | CarbamazepineSodium ValproateLamotrigine | Lithium carbonate and Lithium citrate | e.g. Selective serotonin re-uptake inhibitors (SSRIs)  |
| *\*While antidepressants are used in bipolar disorder, these are beyond the scope of this article; in general they do not require similar monitoring as that of antipsychotics or mood stabilisers and will not need any additional laboratory tests than what is covered under monitoring of bipolar disorder itself.\*\*Also available in IM depot preparation. Monitoring requirements for depot preparations are the same as for oral antipsychotic preparations, though they are usually monitored in a specialist setting.**\*\*\* Whilst Amisulpride is listed as a SGA, its mechanism of action is more aligned to those within the FGA group**\*\*\*\*Monitored throughout its use by specialist mental health units* |

**Why is physical and metabolic monitoring important?**

Our data illustrates that regular blood testing according to guidance can minimise adverse clinical outcomes in both physical6-8 and mental9 health conditions. The importance of physical health checks is emphasised in the NHS Mental Health Implementation Plan.10,11

Antipsychotics: Metabolic side-effects appear particularly common with some SGAs and extrapyramidal/movement side-effects (parkinsonism and akathisia) are more common with FGAs. Some medications (e.g. clozapine, olanzapine, quetiapine) are strongly linked to weight gain, hyperglycaemia and raised triglycerides,12 with quetiapine therapy being a particular risk factor for metabolic syndrome. Other agents (e.g. amisulpiride, risperidone, paliperidone, haloperidol, sulpiride) cause hyperprolactinaemia.12-14 However, drug-induced hyperprolactinaemia should be differentiated from physiological causes (e.g. pregnancy, lactation) and from benign macroprolactinaemia. Glucose and lipid dysregulation are particularly important, as metabolic syndrome, hyperglycaemia, type 2 diabetes and dyslipidaemia are common co-morbidities in people with BD.15,16 Some antipsychotics are associated with prolonged QT interval which can increase the risk of ventricular arrythmias and sudden cardiac death.17 Those at highest risk include haloperidol, quetiapine, amisulpride and chlorpromazine.18 However, there is significant inter-individual variation in the response of a patient to a drug and therefore an individualized approach to monitoring needs to be applied which takes into account baseline QTc duration and its changes after a drug was introduced. Furthermore, risk increases with higher doses and in those on a combination of agents.

In terms of blood dyscrasias, neutropenia in patients on clozapine has received the most attention.13 While its incidence appears generally lower with other antipsychotics, some studies suggest rates may be similar,19 suggesting, in our view, that regular monitoring is prudent across all agents.

Anticonvulsants: Monitoring generally focuses on hepatic impairment (particularly with valproate), blood dyscrasias (more commonly thrombocytopenia in valproate-treated patients) and weight gain.20 Dose-dependent mild thrombocytopenia (platelets <150x109/L) is present in ~20% of patients on valproate, but is only symptomatic in a minority (generally if platelets <50x109/L).21 Mild anaemia occurs in <5% and persistent leucopenia in 2% of carbamazepine-treated patients.21 Asymptomatic transaminase elevation during both valproate and carbamazepine treatment is common (~40% of patients on valproate), but hepatological complications leading to treatment discontinuation are infrequent. While not subject to routine monitoring, the main serious acute medical risk for valproate is pancreatitis, which can be fatal, rather than hepatic impairment, which is almost always reversible. Stevens Johnson syndrome can occur in patients taking lamotrigine. Weight gain affects ~50% of people on valproate, and can be significant (>10% weight gain);22 a factor of which our patient contributor was not made aware. ..

Teratogenicity is a particularly important risk for those on anticonvulsants, particularly valproate.23 Pre-conception counselling and advice regarding effective contraception is essential for all women of childbearing age (*vide infra*).24

Lithium: Lithium toxicity can warrant immediate treatment – and is relatively common; values of ≥1.5 mmol/L and ≥2.0mmol/L occurring in ~1.0% and ~0.3% of cases, respectively.25 Long-term lithium use can cause hypothyroidism (~4% with clinical hypothyroidism though abnormal laboratory values may occur in up to 25%), chronic renal impairment (1-5% after 10-20 years of treatment, interacting with effects of normal aging on GFR) and parathyroid abnormalities (4.3-6.3%).26 Importantly, deterioration in renal function affects lithium clearance leading to increased risk of toxicity.27

Antidepressants: Use of SSRIs is widespread and, in some cases, can trigger an episode of mania as our patient’s story suggests. SSRIs are relatively well tolerated, though some are associated with weight gain, QT interval prolongation and electrolytes imbalances.28 Older antidepressants such as tricyclics are not as commonly prescribed due to side-effects and toxicity in overdoses.

**How is therapy initiated in secondary care?**

In the UK, pre-treatment screening and immediate post-initiation monitoringof physical and metabolic parameters related to bipolar disorder-associated therapies are generally managed under specialist mental health teams before transferal to general practitioners under Effective Shared Care Agreements (local agreements between specialist services and GPs). However, primary care physicians play a critical role in the early stages as well as ongoing management of bipolar disorder, particularly in cases of type 1 bipolar disorder (as in our patient perspective). Much of early-stage assessment reflects longer term monitoring but with increased frequency (see Table 1), until steady-state is achieved (usually up to 3 months).

What do guidelines say about long-term monitoring requirements?

Table 1 provides a collated summary of monitoring recommendations from UK24,28-31 and international3,16,32,33 guidelines. This uses the UK NICE guidelines as a starting point. Supplemental Table 1 includes details of how other guidelines differ from those cited in NICE, focusing on longer-term monitoring. For more detailed information, please refer to your appropriate national guidelines.

Most recommendations for metabolic and physical health monitoring relate to commonly requested blood tests (U&E/eGFR, FBC, LFT, lipids, glucose/HbA1c) and clinical measurements (BP, BMI, waist circumference), along with some drug-specific tests such prolactin and TFT (Table 1). For those on any antipsychotic and/or anticonvulsant, offer annual checks as described in Table 1. For those on lithium therapy, offer 6-monthly monitoring with additional 3 monthly serum lithium testing in those aged >65 years. For SSRIs, UK guidance for monitoring in people with depression suggests 3-monthly U&E assessment,31 though this was not included in the bipolar disorder section of the guidance and, in our experience, this is rarely performed in people with bipolar disorder. Ongoing monitoring is only required in those showing signs of, or at risk of, hyponatraemia such as the elderly.28

Refer any woman with bipolar disorder on medication who plans to become pregnant for pre-conception counselling by a specialist, preferably perinatal, mental health service. Refer those that become pregnant urgently to specialist, preferably perinatal mental health services, to discuss risk versus benefits of ongoing use of medication. Due to teratogenicity risks, ensure that any woman of childbearing potential that is taking valproate is aware of the requirements of the Pregnancy Prevention Programme and complete the Annual Risk Acknowledgement Form together with them.24 23

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| **What might a routine monitoring appointment look like?** |
| Once stabilised on treatment, the physical health monitoring for people with bipolar disorder should include an annual check of blood pressure, body mass index and waist circumference together with measurement of HbA1c, random lipids and U&E. This is in addition to any specific drug level monitoring described in Table 1. If the patient is taking an antipsychotic agent there should also be a check for any manifest extrapyramidal symptoms or akathisia.The NHS England *Improving the Physical Health of People with Serious Mental Illness* toolkit provides information on the key elements of an effective monitoring programme.34 |

There is increasing evidence that conformity to monitoring guidance in many long-term conditions is sub-optimal, with examples of both over- and under-testing. 25,35-38 The reasons for this and tips on how to improve monitoring are provided in Supplemental Figure 1.

**Managing abnormal laboratory test results**

Offer a further clinical assessment to all patients with abnormal results/ Most blood test abnormalities are mild and/or transient, sometimes requiring repeat monitoring to assess trends and clinical follow-up depending on subsequent results.24,29 However, examples where more urgent action or referral are indicated are shown in Table 1.

Antipsychotics: Most adverse events requiring action involves further investigation or interventions (e.g. statins in persistent hyperlipidaemia, medication/lifestyle advice in hyperglycaemia).39 Severe cases (e.g. severe hyponatraemia, agranulocytosis, diabetic ketoacidosis) may require immediate emergency department intervention or withdrawal of treatment (Table 1).

Anticonvulsants: Persistent hyper-transaminasaemia is generally reversible with drug discontinuation and rarely warrants referral to hepatology. Carbamazepine carries the risk of agranulocytosis, requiring immediate cessation and urgent referral to emergency services.28 Moderate hyponatraemia may require dose reduction or gradual withdrawal while severe cases would require immediate intervention.

Lithium: For persistent derangement in thyroid, referral to appropriate specialist services, treating hypothyroidism or medication review may be required. In patients with compromised renal function (eGFR <60 mL/min/1.73m2 or showing a significant downward trend based on local assay performance), some studies recommended gradual medication withdrawal and serum lithium carefully monitored due to the increased risk of lithium toxicity.27 However, some suggest that lithium therapy can be continued even with moderately low eGFR if there is clinical benefit.40 Immediate contact with emergency services is only necessary during acute toxicity, or severe hypercalcemia.

Antidepressants: The most common aspects to be aware of, according to guidance, are the risk of prolonged QT-interval and weight gain.28

Risk of hyponatremia is low and regularly U&E monitoring is rarely performed. However, in the event of hyponatraemia, U&E should be checked every 3 months.

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**Prioritising monitoring in a resource-poor scenario**

The impact of the SARS-CoV-2 pandemic highlighted challenges for ongoing drug monitoring with general practitioners and mental health services needing to prioritise blood testing services whilst ensuring patient safety.2 In this context, there may be a case for less frequent monitoring in people with stable drug levels without compromising safety.25,41,42 In patients on antipsychotics or anticonvulsants, maintain annual ongoing monitoring wherever possible, particularly for U&E (risk of hyponatraemia with antipsychotics) and FBC (risk of agranulocytosis). However, for lithium, those in whom previous results have remained stable over time and who have adequate renal function, it could be possible to extend monitoring to annually.26,42

In our area, we developed a nurse-led service, commissioned by primary care and run by specialist care (but with close links to primary care) whereby all severely mentally ill patients including those with bipolar disorder are offered annual physical health review by a dedicated, community-based nurse team. They input results to both GPs and specialist mental health unit systems (thereby avoiding the duplication as experienced by our patient example), and liaises with the appropriate specialists when results are abnormal. This maximises efficiency and communication whilst minimising the risks of duplicated appointments, as experienced by our patient contributor. Examples of similar initiatives are described in the NHS England *Improving the Physical Health of People with Serious Mental Illness* toolkit developed by the Royal College of Psychiatrists.34

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| **What you need to know*** For each patient with bipolar disorder, assess whether appropriate monitoring of potential adverse effects of medications is up-to-date.
* Watch for: (i) Lithium - signs of toxicity, especially if renal function is deteriorating, (ii) Antipsychotics - extrapyramidal side-effects and signs of metabolic syndrome, (iii) Anticonvulsants - agranulocytosis for carbamazepine, pancreatitis for valproate and Stevens Johnson syndrome for lamotrigine. Inform patients of how to look for these signs.
* Ensure women of childbearing age with bipolar disorder are offered pre-conception counselling by a specialist to discuss risk and benefits of ongoing use of medication. For those on valproate, ensure that they are enrolled in the Pregnancy Prevention Programme.
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| **Education into practice*** How do you know if your monitoring practice conforms to guidance? What systems do you have in place to allow you to assess this?
* How do you engage with patients to ensure that monitoring systems and processes meet their needs?
* What simple things could you do to improve monitoring practice? The underlying causes for the lack of conformity and tips or how to improve monitoring practice are included in Supplemental Figure 1.
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**Table 1 Recommended monitoring tests in people on drug treatments for bipolar disorder** (from UK National Institute for Health and Care Excellence guidelines and British National Formulary assessments of class- and drug-specific side effects)

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| **Drugs** | **Test/ measurement** | **Baseline tests required (prior to initiation)** | **Initiation: test intervals (if applicable)** | **Long-term monitoring frequency (if applicable)** | **Prevalence of abnormal results(class effects)** | **Prevalence of abnormal results(drug-specific effects)** | **Action limits** | **Action for significant abnormal results(Review medication class and dosages, otherwise repeat, review or specialist referral as required)** |
| **ANTI-PSYCHOTICS:**Olanzapine, Risperidone, Paliperidone, Quetiapine, Asenapine, Aripiprazole, Cariprazine, Lurasidone, Amisulpride, Clozapine, Haloperidol, Flupentixol, Zuclopenthixol**,** Chlorpromazine, Sulpiride | U&E | √ |   | annually |   | HyponatraemiaUncommon: Quietapine, LurasidoneSIADHRare: Haloperidol, Risperidone, Paliperidone | Na <130 mmol/L | Hyponatraemia: In moderate cases (121-129 mmol/L), consider dose reduction or gradual withdrawal. If severe (<120 mmol/L), suggest immediate referral to Emergency Department |
| Prolactin | √ | 6, 12 months | annually | Hyperprolactinaemia, gynaecomastiaCommon | Hyperprolactinaemia, gynaecomastiaVery common: Risperidone, Amisulpride, Paliperidone and first generation antipsychotics | >700 mIU/L | > 2500 refer to specialist to rule out prolactinoma |
| TFT | √ |   |   |   | HypothyroidismCommon: QuetiapineRare: Cariprazine | TSH outside local reference range | Hypothyroidism: If persistent: consider referral to endocrinology |
| HbA1c or FPG | √ | 3, 12 months | annually | HyperglycaemiaCommon | HyperglycaemiaVery common: Olanzapine, Clozapine | FPG ≥5.5 mmol/LHbA1c >42 mmol/mol | Hyperglycaemia: Suggest conservative measures (lifestyle advice, etc) upon first detection. If persistent, consider hypoglycaemic agents |
| random lipids | √ | 3, 12 months | annually |   | DyslipidemiaCommon: Olanzapine, Clozapine | Total cholesterol >5 mmol/LHDL <1 mmol/L (males), <1.2 mmol/L (females)LDL >3 mmol/LTriglycerides >2.3 mmol/LTotal:HDL ratio >6 | Dyslipidemia: If persistent, consider use of statins |
| LFT | √ |   | annually |   | Hepatic disordersUncommon: HaloperidolRare: Olanzapine, QuietapineJaundiceRisperidone, Flupentixol | Transaminases >2x ULNTotal bilirubin >20 µmol/LAlbumin: <30 g/L | Deranged LFTs: If severe and/or persistent: consider withdrawal and referral to hepatology  |
| FBC | √ |   | annually | Leucopenia, NeutropeniaCommon | ThrombocytopeniaUncommon: Risperidone, Quietapine, PaliperidoneRare: Olanzapine, FlupentixolAnaemiaUncommon: Quietapine, CariprazineEosinophiliaCommon: OlanzapineUncommon: CariprazineRare: Lurasidone | white cells: <3.5 x 109/Lneutrophils <1.6 x 109/Lplatelets: <140 x 109/Leosinophils: >0.5 x 109/LHb: <120 g/L | Severe leucopenia (agranulocytosis): suggest immediate withdrawal of medication and refer to Emergency Department |
| BMI | √ | weekly for 6 weeks, 3 months, 12 months | annually | Weight gainCommon | Weight lossCommon: HaloperidolWeight gainOlanzapine, Clozapine |   | Weight gain: Consider conservative measures (lifestyle advice) |
| Waist circumference | √ | 3, 6, 12 months | annually |   |   |   | Weight gain: Significant weight gain in first 6 weeks – Review choice of antipsychotics.Consider conservative measures (lifestyle advice) |
| ECG | √ (for high CV risk patients and certain medication, e.g. Haloperidol) | 3 months | annually | QT interval prolongation, ArrhythmiasRisk varies between antipsychotics |   | QTc > 440 for men and >460 for female>500 – seek specialist advice  | Arrythmias: discontinue treatment and seek specialist advice |
| BP/pulse | √ | 3, 6, 12 months | annually | HypotensionCommon (dose related) | HypertensionCommon: Risperidone |   | Persistent hypotension: consider reducing dose or discontinuationPersistent tachycardia – consider cardiology review |
| **ANTI-CONVULSANTS:**Carbamazepine, Valproate, Lamotrigine | U&E | √ |   |   | HyponatraemiaCommon | Renal failureUncommon: ValproateRenal impairmentRare: Carbamazepine | Na <130 mmol/LeGFR: <60 mL/min | Hyponatraemia: In moderate cases (121-129 mmol/L), consider dose reduction or gradual withdrawal. If severe (<120 mmol/L), suggest immediate referral to Emergency Department |
| LFT | √ | 6, 12 months | annually |   | Hepatic disordersCommon: valproateRare: Carbamazepine | Transaminases >2x ULNTotal bilirubin >20 µmol/LAlbumin: <30 g/L | Deranged LFTs: If severe and/or persistent: consider withdrawal and referral to hepatology  |
| FBC | √ | 6, 12 months | annually | ThrombocytopeniaCommon | Eosinophilia, LeucopeniaCommon: CarbamazepineAnaemiaCommon: ValproateRare: Carbamazepine |   | Severe leucopenia (agranulocytosis): Suggest immediate withdrawal of medication and refer to Emergency Department |
| BMI | √ | 6, 12 months | annually | Weight gainCommon |   |   | Weight gain: Consider conservative measures (lifestyle advice) |
| Pregnancy Prevention Programme review (Valproate only) | √ |   | annually | TeratogenicityThose who plan to or become pregnant should be referred urgently to a mental health specialist. |   |   |   |
| **OTHER:**Lithium | Serum lithium |   | weekly until stable(at initiation and after dose change) | 6-monthly (3-monthly if over 65 years) | Toxicity, Lack of efficacy, complianceCommon | ≥1.0 mmol/mol (toxicity)<0.4 mmol/mol (efficacy) | Elevated serum lithium (>1.5 mmol/L): Suggest stop immediately and refer to Emergency Department |
| TFT | √ |   | 6-monthly | HypothyroidismCommonHyperthyroidismUncommon | TSH outside local reference range | Abnormal TFT: If persistent, consider referral to endocrinology |
| calcium | √ |   | 6-monthly | HypercalcaemiaCommon | >2.6 mmol/mol | Hypercalcaemia: If persistent but mildly raised (2.6-3.0 mmol/L) consider further investigations and possible referral to endocrinology. If severely raised (>3.0 mmol/L), stop medication immediately and refer to Emergency Department |
| eGFR/U&E | √ |   | 6-monthly (more frequently if renal impairment) | Renal impairmentCommon | eGFR: <60 mL/min | Renal impairment: If eGFR 60-90 mL/min, monitor serum lithium and eGFR frequently. If eGFR is <60, consider withdrawal and seek specialist advice. |
| BMI | √ |   | 6-monthly | Frequency not known |   | Weight gain: Consider conservative measures (lifestyle advice) |
| ECG (if CVD risk present) | √ |   |   | Frequency not known |   | Arrythmias: discontinue treatment and seek specialist advice |
| **ANTIDEPRESSANTS** | U&E | √ | at 2-4 weeks | Ongoing monitoring required if signs of hyponatraemia or in high-risk patients. |   |   |   |   |
| BMI | √ |   |   |   |   |   |   |
| ECG | √ (For patients with high-risk of CVD) |   |   |   |   |   |   |
| BP (for Duloxetine or Venlafaxine) | √ (hypotension needs to be controlled) |   |   |   |   |   |   |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  | *British National Formulary definitions of prevalence:Rare: <1%Uncommon: 0.1-1%Common: 1-10%Very common: >10%* |  |  |