DIVISION OF PUBLIC AND BEHAVIORAL HEALTH
CLINICAL SERVICES

Control #	Rev. Date:	Title:	Effective Date: 11/2023
_____	11/2023	Therapeutic Plasma-Serum Level Guide for Antipsychotics and Mood Stabilizers	Next Review Date: 11/2025

1.0 POLICY:

The Division of Public and Behavioral Health (DPBH) Clinical Services Branch shall establish guidelines in prescribing antipsychotics and mood stabilizers.

2.0 PURPOSE:

The purpose of this policy is to provide guidance to the DPBH medical staff in prescribing antipsychotics and mood stabilizers as evidence-based treatment.

3.0 SCOPE:

DPBH Clinical Services Branch.

4.0 DEFINITIONS:

4.1 **Therapeutic Threshold** – is generally defined by a response threshold below which one is unlikely to find adequate response.

4.2 **Maximum Plasma-Serum Level** – is defined by the upper limit of the laboratory range or the laboratory alert level.

4.3 **Point of Futility** – is defined by the plasma level of medication beyond which only a minuscule fraction of patients will respond to on-going titration.

4.4 Untherapeutic response is defined by the following findings:

4.4.1 When adverse effects arise at low doses (e.g. as might be seen with poor metabolizers);

4.4.2 When no adverse effects or efficacy are seen at standard doses to help rule out kinetic failure (due to ultra-rapid metabolism) or adherence issues;

4.4.3 When there is decompensation or behavior change in a previously stable patient.

5.0 REFERENCES:

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5.2 Meyer JM, Cummings MA, Proctor G, Stahl SM. Psychopharmacology of persistent violence and aggression. Psychiatric Clinics of North America 2016:39:541–56

5.3 Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, Chabner B. Knollmann B. eds.

5.4 Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Edition. Chicago, Illinois: McGraw-Hill; 2017:in press

5.5 Castro VM, Roberson AM, McCoy TH, et al. Stratifying risk for renal insufficiency among lithium-treated patients: an electronic health record study. Neuropsychopharmacology 2016:41:1138-43

5.6 Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord 2014:16:409-31

5.7 Post RM, Ketter TA, Uhde T, Ballenger JC. Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. CNS Drugs 2007:21:47-71

5.8 Letmaier M, Painold A, Holl AK, et al. Hyponatraemia during psychopharmacological treatment: results of a drug surveillance programme. Int J Neuropsychopharmacol 2012:15:739-48

5.9 Vasudev A, Macritchie K, Watson S, Geddes JR, Young AH. Oxcarbazepine in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev 2008: Cd005171

5.10 Kim YS, Kim DW, Jung KH, et al. Frequency of and risk factors for oxcarbazepine-induced severe and symptomatic hyponatremia. Seizure 2014:23:208-12

5.11 Meyer JM., Stahl SM. The clinical use of antipsychotic plasma levels. Cambridge University Press 2021

6.0 PROCEDURE:

6.1 Once the Therapeutic Threshold is exceeded, if there is inadequate response and no tolerability issues, the antipsychotic should be titrated until one of three endpoints is reached:

- 6.1.1 Intolerability;
- 6.1.2 Point of Futility;
- 6.1.3 Maximum Level as reported by the lab.

6.2 It is recommended that the medical staff consider ordering Plasma-Serum Levels for antipsychotics and mood stabilizers:

- 6.2.1 When the patient has an optimal drug response to benchmark the drug level(s); or
- 6.2.2 When the patient has untherapeutic response to antipsychotics and/or mood stabilizers.

6.3 Plasma-Serum Levels for antipsychotics should be measured 12-hour post dose for oral formulations. Plasma-Serum Levels for long-acting injectable (LAI) antipsychotics should be measured just before the next injection.

6.4 If levels above the Maximum Level reported by the lab:

- 6.4.1 Do not reflexively reduce medication dose(s).
- 6.4.2 Document whether the patient is tolerating the particular plasma level.
- 6.4.3 If there is suspicion of lab error, the level should be repeated.
- 6.4.4 If the repeat level remains above the Maximum Level, one should investigate whether the patient needs this high level for response.
- 6.4.5 If not, the dose should be reduced by no more than 5% per month to prevent unmasking of super-sensitivity psychosis or other rebound effects.

6.5 Antipsychotic Levels and average Expected Plasma Levels (in ng/ml) for Given Oral Doses

Medication	**Therapeutic Threshold** ng/mL	**Maximum Level** ng/mL	**Point of Futility** ng/mL
Aripiprazole Average Expected Level = 12 x oral dose (mg/d)	110	1000	500

Asenapine (sublingual) Average Expected Level = 0.15 x oral dose (10 mg/d) or 0.2 x oral dose (20 mg/d)	1.0	10	
Brexpiprazole Average Expected Level = 18 x oral dose (mg/d) for CYT 2D6 EM Average Expected Level = 46 x oral dose (mg/d) for CYT 2D6 IM	36	280	
Cariprazine Average Expected Level = 1.91 x oral dose (mg/d)	5.6	40	
Chlorpromazine Average Expected Level = 0.06 x oral dose (mg/d)	3-30	600	100
Clozapine Male nonsmoker: Average Expected Level = 1.08 x oral dose (mg/d) Male smoker: Average Expected Level = 0.67 x oral dose (mg/d) Female nonsmoker: Average Expected Level = 1.32 x oral dose (mg/d) Female smoker: Average Expected Level = 0.8 x oral dose (mg/d)	350	1000	1000
Fluphenazine Nonsmokers: Average Expected Level = 0.08-0.1 x oral dose (mg/d)	1.0	15	4.0

Smokers: Average Expected Level = 0.06 x oral dose (mg/d)			
Haloperidol Average Expected Level = 0.78 x oral dose (mg/d)	2.0	15	18
Loxapine Average Expected Level = 0.22 x oral dose (mg/d)	3.8	20	18.4
Lurasidone Average Expected Level = 0.18 x oral dose (mg/d)	7.2	120	
Olanzapine Nonsmoker: Average Expected Level = 2.0 x oral dose (mg/d) Smoker: Average Expected Level = 1.43 x oral dose (mg/d)	23	100	150
Paliperidone Average Expected Level = 4.09 x oral dose (mg/d)	20	120	90
Risperidone + 9-OH Risperidone Average Expected Level = 7.0 x oral dose (mg/d)	15	120	112
Perphenazine Average Expected Level = 0.04 x oral dose (mg/d) for CYT 2D6 EM Average Expected Level = 0.08 x oral dose (mg/d) for CYT 2D6 IM	0.81	5	5.0
CYP: Cytochrome P450 **EM**: Extensive metabolizer **IM**: Intermediate metabolizer			

6.6 Mood Stabilizer Serum Levels

Divalproex, valproic acid		
Acute	100 mcg/mL	120 mcg/mL
Maintenance	80 mcg/mL	120 mcg/mL
Lithium		
Acute	1.0 mEq/L	1.4 mEq/L
Maintenance	0.8 mEq/L 0.6 meq/L in elderly	1.2 mEq/L (see III.6.b section)
Carbamazepine		
Acute	9 mcg/mL	12 mcg/mL
Maintenance	6 mcg/mL	12 mcg/mL

6.7 Principles of Using Mood Stabilizer Serum Levels

6.7.1 For lithium and divalproex, different levels are used for acute symptoms than for maintenance. For patients with severe and/or persistent symptoms it is recommended that maintenance levels be no lower than the midpoint of the maintenance range cited in the section III.6.

6.7.2 Chronic maintenance lithium levels greater than 1.0 incur greater risk for renal dysfunction and should only be used transiently whenever possible. In the elderly, the upper optimal limit should be 0.8 meq/L. For acute mania, levels up to 1.4 may be necessary. Once the patient is euthymic and stable, the level can be lowered.

6.7.3 The use of carbamazepine is strongly discouraged for several reasons:

6.7.3.1 It will lower plasma antipsychotic levels 30%-80% thereby endangering the patient and others on the unit if antipsychotic levels are not appropriately adjusted within 10-14 days of starting carbamazepine;
6.7.3.2 It is less effective than lithium or VPA;
6.7.3.3 It carries a risk of hyponatremia.

6.7.4 Oxcarbazepine is not recommended to be used within the DPBH as a mood stabilizer for the following reasons:

6.7.4.1 It is ineffective for acute mania and for inpatient aggression;

6.7.4.2 There is no long term data on suicidality risk reduction or risk for mania relapse;
6.7.4.3 There is no defined dose or serum level range;
6.7.4.4 It carries a greater risk for hyponatremia than does carbamazepine.

7.0 ATTACHMENTS: N/A

8.0 IMPLEMENTATION OF POLICY:

Each Division agency shall implement this policy and may develop specific written protocols and procedures as necessary to do so effectively.

EFFECTIVE DATE: _____
DATE APPROVED BY DPBH ADMINISTRATOR: _____
DATE APPROVED BY THE COMMISION ON BEHAVIORAL HEALTH: _____