Appendix -- Therapeutic Plasma-Serum Levels for Antipsychotics and Mood Stabilizers

NOTE: Directive statements and procedures in this chapter are informational and advisory in nature.

I. General Comments - When to Obtain Steady State Drug Levels

A. When the patient has an optimal drug response to benchmark the drug level(s);

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

C. 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;

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

E. Definition of the **Point of Futility:** What most laboratories report as the upper end of the therapeutic range is often not evidence based, and in some instances is not a therapeutic level but that derived from kinetic studies. (reference range = mean +/- 2SD) The **Point of Futility** embodies the following concepts:
   - Assuming the patient is tolerating the medication, pursuing a level up to the **Point of Futility** is not unsafe.
   - The chance of response at levels greater than the **Point of Futility** is < 5%. Nevertheless, rare patients may require higher than expected plasma concentrations to maintain benefit. In such cases, the plasma concentration should be gradually lowered and if signs and symptoms emerge above the point of futility, this should be documented in the patient's record and the plasma concentration should then be titrated to its effective concentration.

II. Using Antipsychotic Plasma Levels - Principles [1]

A. The **Minimum Level** defines a response threshold below which one is unlikely to find adequate response, although there are always exceptions.

B. Once the **Minimum Level** is exceeded, if there is inadequate response and no tolerability issues, *the antipsychotic should be titrated until one of three endpoints is reached:*

1. Intolerability

2. **Point of Futility** (response probability < 5%)

3. Marked clinical improvement

Comment: **if the clinician does not see at least minimal improvement 2 weeks after a dose is increased, there is low likelihood that the patient will be a responder after 6 weeks. Do not leave a nonresponding patient on the same dose for months waiting for 'late response.'** Even for clozapine, when patients finally arrive at a dose (and level) when the do respond, this occurs on average 17 days after the dose increase.

III. The Point of Futility

If levels above the **Point of Futility** cited here are obtained, do not reflexively reduce medication doses.

A. First document whether the patient is tolerating the particular plasma level.

B. If there is suspicion of lab error, the level should be repeated.

C. If the repeat level remains above the **Point of Futility**, one should investigate whether the patient needs this high level for response.

D. 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.

E. Be mindful that what laboratories report as the upper end of the therapeutic range is often not evidence based. The levels cited here as the Point of Futility are established based on an extensive review of the published literature and are supported by the latest consensus recommendations.

Table 1. Antipsychotic Levels and average Expected Plasma Levels (in ng/mL) for Given Oral Doses[2]

MEDICATION	MINIMUM Response Threshold	POINT OF FUTILITY
Aripiprazole Average Expected Level = 11 x oral dose (mg/d)	110 ng/mL	500 ng/mL
Clozapine Nonsmokers: • Male: Average Expected Level = 1.08 x oral dose (mg/d) • Female: Average Expected Level = 1.32 x oral dose (mg/d)	350 ng/mL	1000 ng/mL
Fluphenazine Nonsmokers: Average Expected Level = 0.08 to 0.10 x oral dose (mg/d)	0.8 ng/mL	4.0 ng/mL
Haloperidol Average Expected Level = 0.78 x oral dose (mg/d)	2.0 ng/mL	18 ng/mL
Olanzapine Nonsmokers Average Expected Level = 2.0 x oral dose (mg/d)	23 ng/mL	150 ng/mL
Paliperidone Average Expected Level = 4.09 x oral dose (mg/d)	20 ng/mL	90 ng/mL
Risperidone + 9-OH Risperidone Average Expected Level = 7.0 x oral dose (mg/d)	15 ng/mL	112 ng/mL
Perphenazine Average Expected Level = 0.04 x oral dose (mg/d) Average Expected Level = 0.08 x oral dose (mg/d) (CYP 2D6 Poor Metabolizers)	0.81 ng/mL	5.0 ng/mL

Reference: Meyer JM, Stahl SM. Chapter 18: Therapeutic threshold, point of futility, oral concentration-dose relationships. **The Clinical Use of Antipsychotic Plasma Levels - Stahl's Handbooks.** New York, NY: Cambridge University Press, 2021.

IV. Using Mood Stabilizer Serum Levels—Principles

A. **Lithium and Divalproex/Valproic Acid are the most effective mood stabilizers.**

1. For both lithium and divalproex, different levels are used for acute symptoms than for maintenance. [Please see table on next page.]

2. Within the DSH system patients tend to be more ill, so we recommend that maintenance levels be no lower than the midpoint of the maintenance range cited in the literature (see below).[3]

3. Chronic *maintenance* lithium levels > 1.0 incur greater risk for renal dysfunction and should only be used transiently whenever possible.

    a. In the *elderly*, the upper optimal limit should be 0.8 mEq/L.

    b. For *acute mania,* levels up to 1.4 may be necessary.

    c. Once euthymic and stable, the level can be lowered. [4]

B. **Carbamazepine is strongly *dis*couraged for several reasons**.

1. It will lower plasma antipsychotic levels by 30 – 80% and could destabilize the patient, thereby endangering others on the unit.

    Hence, the dosages of antipsychotics need to be adjusted within 10-14 days of starting carbamazepine to maintain therapeutic plasma antipsychotic levels. [5]

2. It is less effective than lithium or VPA. [6]

3. It carries a risk of hyponatremia. [7]

C. **Oxcarbazepine should never be used within DSH as a mood stabilizer.**

1. It is *ineffective* for acute mania and for inpatient aggression.

2. There is no long-term data on suicidality risk reduction or risk for mania relapse. [8]

3. There is no defined dose or serum level range. [8]

4. It carries a greater risk for hyponatremia than carbamazepine. [9]

Table 2. Plasma Levels of Effective Mood Stabilizers [3]

DIVALPROEX/VALPROIC ACID		
	Minimum Response Threshold	Point of Futility
ACUTE	100 mcg/mL	120 mcg/mL
MAINTENANCE	80 mcg/mL	120 mcg/mL
LITHIUM		
	Minimum Response Threshold	Point of Futility
ACUTE	1.0 mEq/L	1.4 mEq/L
MAINTENANCE	0.8 mEq/L 0.6 mEq/L (elderly)	1.2 mEq/L (see IV.A.3.c. above)
CARBAMAZEPINE		
	Minimum Response Threshold	Point of Futility
ACUTE	9 mcg/mL	12 mcg/mL
MAINTENANCE	6 mcg/mL	12 mcg/mL

References:

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