Therapeutic Drug Monitoring

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Introduction

Therapeutic drug monitoring means measuring blood levels of medications to guide dosing and detect toxicity or nonadherence. Its usefulness is the subject of continuing debate. The only medications for which drug levels can actually help you fine tune dosing are lithium, valproic acid, carbamazepine, clozapine, and nortriptyline. For other drugs in psychiatry, blood levels are useful only to see if the patient is adherent or if they have a genetic variation affecting there ability to metabolize the drug normally.

Reasons to order drug levels

- **Fine tune the dose.** For a very few drugs in psychiatry, we have some evidence that certain serum levels are correlated with efficacy—these are lithium, valproic acid, carbamazepine, clozapine, and nortriptyline.
- **Understand poor tolerability**. Some patients seem to have significant side effects to low doses of medications, and for such patients you might consider ordering serum levels just to see if the serum level is very high. If this is true, your patient may be a genetically poor metabolizer (which you can investigate with genetic testing) or there may be a drug-drug interaction.
- **Understand poor response.** If your patient is consistently not responding to medications at robust doses, it's possible that they are not adherent, that they are genetically ultra-rapid metabolizers, or that there is a drug interaction causing rapid metabolism of the medication. Ordering TDM and finding atypically low blood levels can help you decide what to do next.

Practical issues

The best time to draw a drug level is during steady-state, which is five half lives after initiating the medication or after making a dosage change; for most medications below, this means about 5 days. You should measure the trough level (the lowest level), which is best done right before a dose is taken (eg., if the drug is taken in the morning, draw the blood before the morning dose; if it is given twice a day, draw it at least 12 hours after the last dose.)

TDM to fine-tune dosing

For the following medications, there is reasonably good evidence correlating specific ranges of blood levels with therapeutic efficacy. The usual procedure is to titrate the medication up to the standard recommended dosage, then order blood levels to guide any further titration.

- Lithium
    - Clinical efficacy: Widely accepted evidence of the following:
        - 0.6-0.8: Correlated with prevention of depression
        - 0.9-1.2: Correlated with treatment and prevention of mania
    - Toxicity
        - Levels above 1.2 are correlated with side effects and toxicity, though select patients may require higher blood levels for a clinical response without becoming toxic.
- Valproic acid
    - Clinical efficacy: 50-100 mcg/mL for bipolar disorder, though correlation is weak

    - Toxicity: Levels above 100 mcg/mL increase risk of side effects
- Carbamazepine
    - Clinical efficacy: 4-12 mcg/mL for bipolar disorder
    - Toxicity: Levels above 12 mcg/mL increase risk of side effects
- Clozapine
    - Clinical efficacy: 350 ng/mL is generally considered the minimal blood level for a response. There is some limited evidence that efficacy falls off above 600 ng/mL but there are many individual patients who require higher doses. Note that some labs also report norclozapine levels, but this is not useful for making dosing decisions, so just ignore that value if you see it.
    - Toxicity: Levels above 1000 ng/mL increase risk of side effects, especially seizures.
- Nortriptyline
    - Clinical efficacy: 50-150 ng/mL for depression
    - Toxicity: Levels above 150 ng/mL increase risk of side effects
- Clomipramine
    - Clinical efficacy: clomipramine 50-250 mcg/L; desmethylclomipramine 150-350 mcg/L; Total 200-500 mcg/L
    - Toxicity: Levels above 500 mcg/L (total) increase risk of side effects

TDM to assess non-response or toxicity

- The following medications and classes of medications have no conclusive evidence of a correlation between blood levels and efficacy. The only reason to draw their levels is in cases of non-response, suspected overdose, or specific side effects.
    - Antipsychotics other than clozapine
    - Antidepressants other than tricyclics
    - Lamotrigine