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Commentary

Why patients may not respond to usual recommended dosages

3 variables to consider when prescribing antipsychotics

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Psychiatrists may consider using higher than usually recommended dosages of antipsychotics when faced with nonresponse. In this issue (*page 30*), Pierre et al[1] carefully and thoughtfully discuss the pros and cons of this practice in patients with schizophrenia. Having reviewed that article, I thought CURRENT PSYCHIATRY's readers might benefit from a theoretical framework for analyzing drug response.

'USUAL' VS 'UNUSUAL' PATIENTS

A clinical trial for drug registration is, in essence, a population pharmacokinetic study whose goal is to determine the usual dosage for the usual patient in the trial. Many patients seen in clinical practice, such as those with treatment-refractory psychotic disorders, are typically excluded from registration trials. Thus, the usual registration trial patient may be an unusual patient in a clinician's practice, and the trial's usual dosage may not produce an adequate response for the clinician's usual patient. How, then, might a clinician approach inadequate response, except by:

- blindly exceeding the usually recommended dosage
- switching among available drugs
- adding drugs to create a complex cocktail?

This commentary dissects why a patient might not benefit from the usual recommended dosage and how that could lead to different courses of action.

Equation 1. Three variables (*Table*) determine response to any drug:

- affinity for and intrinsic action on a regulatory protein (such as a receptor)
- concentration (amount of drug reaching the site of action)
- biological variance, which can shift an individual's dose-


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Dr. Preskorn's Web site at www.preskorn.com offers more information on this topic.

Table

3 variables that determine patient response to any drug

Equation 1

Effect	=	Affinity for and intrinsic activity at a site of action	X	Drug concentration (see Equation 2) Absorption Distribution Metabolism Elimination (ADME)	X	Biological variance Genetics Age Disease Environment (internal) (GADE)

Equation 2

Drug concentration	=	dosing rate/clearance

response curve relative to that of the "usual" patient, making that individual more or less sensitive to the drug's effects.[2]

Equation 2. Drug concentration is dosing rate divided by clearance in a given patient. Dosing rate and clearance are equally important in determining drug concentration—which, in turn, determines the site of action engaged, to what degree, and the patient's response to the drug.

Causes of inadequate response. Nonadherence is a common cause of inadequate response. When a patient repeatedly misses doses or stops taking the drug, the true dosing rate is lower than the prescribed dosing rate, resulting in reduced drug concentration and effect.

Pierre and colleagues focus on the "unusual" patient who does not respond optimally to antipsychotic dosages established in registration trials.[1] As in *Equation 1*, sources of biological variance—genetics, age, disease, and environment (internal)—may distinguish the treatment-refractory patient from the responsive patient. The mnemonic GADE captures these variables:

Genetic variation refers to mutations in regulatory proteins that:

- determine the drug's action (such mutations may change the drug's binding affinity, so that a higher concentration is needed to adequately engage the site)
- determine what drug concentration reaches the site of action (such as drug-metabolizing enzymes that regulate clearance, or transporter proteins that prevent or facilitate the drug's ability to reach the site of action).

Age refers to physiologic changes (pharmacodynamic or pharmacokinetic) that make the patient more or less sensitive to the drug's effects.

Disease refers to differences in organ function related to pathophysiology. Patients with the same clinical presentation (in this case, psychosis) may respond differently to the same drug because they have different underlying pathophysiologies (such as schizophrenic syndrome due to differing genetic causes or to toxins or slow viruses).

Environment (internal) refers to exogenous substances in the body—such as drugs and dietary substances—that can interact with and influence response to other drugs.

Nonpsychiatric disease also can alter response to medication. For example, impaired hepatic, renal, or cardiac function can impair drug clear-

ance, leading to greater-than-usual accumulation. Such a patient can be "sensitive" to the drug and experience a greater effect than is usually seen with the dosage given.

DOSING FOR CLINICAL EFFECT

Psychiatrists commonly titrate dosages based on clinical assessment of response.[3] The clinician increases the dosage if a patient does not improve and has no obvious rate-limiting adverse effects.

Perhaps without realizing it, the clinician is assuming that the dosage is inadequate for a given patient because the concentration is inadequate due to rapid clearance. Other reasons are possible, however, such as:

- the drug is not reaching the site of action
- a mutation at the site of action is altering the drug's binding affinity
- the concentration may be too high, but the resulting adverse effects resemble worsening of the disease being treated. For example, akathisia due to dopamine-2 receptor blockade can present as agitation, and the clinician may increase the dosage when it should be decreased.

In the first two instances, escalating the dosage may be beneficial or cause toxicity. High levels in a peripheral compartment can cause adverse effects that may be silent until they become deadly (such as torsades de pointes). In the third instance, dosage escalation is the wrong step because the level is already too high.

RECOMMENDED DOSAGE RANGE

Principal goals of phase I studies in drug development are to establish the optimal dosage range and a maximum tolerated dosage. This upper limit is rarely, if ever, exceeded in later trials. Because phase I trial results are rarely published, the prescriber often does not know the rationale for a recommended dosing range's upper limit.

Clinicians who escalate a drug's dosage above the recommended range are using an $n=1$ paradigm, in which the patient is his or her own control. Unfortunately, treating one patient at a time cannot detect infrequent (much less rare) adverse events.

Using higher-than-recommended dosages thus exposes patients to unknown risks, with less monitoring than in a typical phase I trial in which subjects are confined to a research unit before, during, and after drug exposure. During the study, participants undergo serial ECGs, laboratory tests, and plasma drug level monitoring.

Therapeutic drug monitoring (TDM) is based on the concept that a meaningful relationship exists between a drug's plasma concentration and its concentration at the site of action. Clinicians can measure the drug's plasma concentration relative to the presumed dosage a patient is taking.

When nonadherence is the reason for nonresponse to usual dosing, TDM measurements of drug concentration would be lower than expected—or nonexistent with complete nonadherence. Rapid clearance, however, can also cause lower-than-expected levels on a given dosage.

So, how can the clinician determine whether the problem is rapid clearance or noncompliance? One way is to repeat the plasma level after arranging for supervised dosing for at least five times the half-life of the drug being measured. A higher level on follow-up would indicate that noncompliance is the likely problem. If the repeat level remains low, then the problem is most likely rapid clearance. In the latter case, the patient would need a higher dosage to achieve the concentrations associated with response in clinical trials.

Although TDM's results are often conceptualized as being relative to a therapeutic range, TDM is fundamentally a means of measuring a patient's ability to clear the drug. If the dosing rate and plasma drug level are known, then the clinician can solve for clearance by rearranging *Equation 2*. Rather than formally solving for clearance, results can be considered as within, below, or above the

continued on page 43

continued from page 40

expected range for the dosage given. The clinician can then adjust the dosage to compensate for clearance that is faster or slower than usual. Thus, TDM allows clinicians to individualize dosages, taking into account the biological variances (*Equation 1*) that affect a patient's ability to clear a specific drug.

TDM has limitations. It cannot assess whether a genetic mutation may be altering a drug's binding affinity at the receptor site or whether the drug is not reaching the target compartment because of an abnormality in distribution mechanisms. Those possibilities would need to be assessed by techniques not available to most clinicians today.

Many psychiatrists think the inability to show a correlation between plasma drug levels and response is a limitation of TDM. That is not a limitation of TDM as much as a reflection on clinical trials of psychiatric drugs. Many such trials fail because of poor "signal-to-noise ratio"—defined as the true specific response to the treatment versus either placebo response or nonresponse due to not having an illness that is responsive to the drug.

Consider instead that the usually effective dosage defines a usually expected plasma drug concentration range associated with response. Further discussion of this topic is beyond the scope of this commentary, but the interested reader is referred to articles at www.preskorn.com, including *Clinical pharmacology of serotonin selective re-uptake inhibitors* (chapter 5); the column, *Understanding dose-response curves in psychiatry;* and the discussion, *Finding the signal through the noise*.

SUMMARY

Based on the review by Pierre et al, the evidence for high-dose atypical antipsychotics' safety and tolerability is not encouraging. These authors found only a modest body of evidence, and most study designs were not rigorous enough to eliminate erroneous conclusions. My intent here is not to advocate the use of higher-than-recommended dosages but to explain reasons why the patient may not respond and to call for more research.

Investigators designing future studies of nonresponse could consider including procedures to first rule out noncompliance and then divide participants into two groups:

- patients who achieved usual plasma drug levels on the usual recommended dosages (normal clearance)
- those who achieved levels below the usual expected range, despite good compliance (rapid clearance).

These two groups could then be randomized to continued exposure to the usual dosing range or higher-than-usual dosing. Patients with rapid clearance would be predicted to have a greater response to higher-than-usual dosing, compared with those with usual clearance.

In the absence of such trials, the clinician should proceed cautiously—if at all—to use higher-than-usual antipsychotic dosages in his or her patients. The prescriber must always consider whether the risks outweigh the potential benefits, taking into account:

- the drug's therapeutic index
- evidence of safety and tolerability problems in the individual patient as the dosage is escalated.

References

1. Pierre JM, Wirshing DA, Wirshing WC. High-dose antipsychotic therapy: Desperation or data-driven? *Current Psychiatry* 2004;3(8):30-7.
2. Preskorn SH. Relating clinical trials to psychiatric practice: part I: the case of a 13-year-old on aripiprazole and fluoxetine. *J Psychiatr Pract* 2003;9(4):307-13. Also available at www.preskorn.com under Columns, Case studies.
3. Preskorn SH. Relating clinical trials to psychiatric practice: part II: the gap between the usual patient in registration trials and in practice. *J Psychiatr Pract* 2003;9(6):455-61. Also available at www.preskorn.com under Columns, Case studies.

Related resources

- Preskorn SH. The recommended dosage range: How is it established and why would it ever be exceeded? *J Psychiatry Pract* 2004;10(4):249-54.