Clinical and Practical **Psychopharmacology**

Practical Psychopharmacology: Using a Knowledge of Pharmacokinetics to More Rapidly Stabilize Patients at Lower Drug Doses

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Three drug dosing strategies can be employed to address dose-dependent drug adverse effects. The usual strategy is to continue the drug but at a lower dose; it would then take 5 half-lives of the drug for the new steady state to be attained and for a dose-dependent adverse effect to correspondingly attenuate. Such slow offset of the adverse effect could be disadvantageous for drugs such as fluoxetine, penfluridol, and cariprazine that have long half-lives. A second strategy is to stop the drug and to resume it at a lower dose when the adverse effect attenuates as the drug blood level falls. This strategy introduces subjectivity in timing the reintroduction of the drug, requires closer patient monitoring, and risks nonadherence and relapse. The third strategy is to stop the drug for a prespecified number of days and to then reintroduce it at a lower dose. From a knowledge of pharmacokinetics, it can be shown that stopping a drug for just 1 half-life and then resuming it at half the dose results in the immediate achievement of steady state; that is, there is no need to wait for 4 additional half-lives as with the usual strategy of dose reduction without dosing interruption. A limitation of this pharmacokinetically driven dosing strategy, however, is that it would work well in the average patient but not in those with outlying pharmacokinetic parameters.

J Clin Psychiatry 2022;83(6):22f14722

To cite: Andrade C. Practical psychopharmacology: using a knowledge of pharmacokinetics to more rapidly stabilize patients at lower drug doses. *J Clin Psychiatry.* 2022;83(6):22f14722.

To share: https://doi.org/10.4088/JCP.22f14722

As competent clinicians, we need to know much about the clinical pharmacology of the drugs that we prescribe. We need to know about their safety and efficacy in different doses as well as about their safety and efficacy in special populations such as the young and old, and those with neurologic, hepatic, renal, and other medical comorbidities. Competent prescribing also requires a knowledge about clinical pharmacokinetics, such as about factors that influence drug absorption, metabolism, and excretion. Two previous articles in this column examined half-life as a special aspect of clinical pharmacokinetics. The first[1] explained basic concepts with the help of clinically relevant examples. The second[2] discussed psychotropic drugs with long half-lives and clinical issues related thereto. The present article discusses a special situation: use of knowledge about the half-life of a drug to more rapidly stabilize drug levels at a lower dose.

Clinical Question

A patient with schizophrenia experiences mild to moderate akathisia with cariprazine at a dose of 6 mg/d. Because the clinical response to cariprazine has otherwise been good, a decision is made to persist with the drug but to reduce the dose to 3 mg/d, at which dose the akathisia is expected to diminish or disappear.[3] What is the best way to quickly and efficiently stabilize the patient at the lower dose?

The Conventional Approach

The conventional approach that is almost universal is to reduce the dose of cariprazine from 6 mg/d to 3 mg/d and to then wait for the expected reduction in the akathisia. There is a problem with this strategy. Cariprazine is 3 drugs in 1: the parent drug cariprazine and its active metabolites desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR). The half-life of cariprazine is 2–4 days. The half-lives of DCAR and DDCAR (which are pharmacologically equipotent to cariprazine) are 1–2 days and 1–3 weeks, respectively. The combined effects of the parent drug and its active metabolites take 4–8 weeks (>12 weeks, in some patients) to reach steady state.[4]

We know that it takes 5 half-lives for a drug to reach steady state levels.[1] This applies to all situations: starting a drug, raising the dose, changing the frequency of administration, lowering the dose, and stopping the drug. So, if we want to reduce the maintenance dose of a drug by half (6 mg/d to 3 mg/d), it will take 5 half-lives to reach the new steady state. Assuming that the effective time to steady state of the combined cariprazine, DCAR, and DDCAR effects is midway between 4 and 8 weeks (that is, 6 weeks) in the average patient, by reverse calculation we estimate that the half-life for the activity of

cariprazine and its metabolites, combined, is one-fifth of 6 weeks, or approximately 8–9 days.

For convenience, let us assume that the half-life of the combined entities is 10 days; this could certainly be true for many patients. So, if we reduce the daily dose of cariprazine from 6 mg to 3 mg, it will take 5 half-lives, or 50 days, for the new steady state to be attained. That is a long time to wait if the patient has dose-related akathisia. Thus, the conventional approach to dose reduction is inefficient with drugs that have long half-lives.

A Stop-and-Resume Approach

An alternative to the conventional approach is to stop cariprazine, wait for the akathisia to abate, and then resume treatment at the lower dose of 3 mg/d with the hope and expectation that this lower dose will be well tolerated. This approach has a large advantage: it permits the resumption of cariprazine at the level of discomfort that is deemed acceptable by the patient. Unfortunately, this approach also has limitations. One limitation is that gradual reduction in akathisia associated with fluctuations in the severity of akathisia may make it hard to pinpoint when exactly it has diminished to an acceptable level; so, cariprazine may be resumed too early, making the tolerability of the lower dose harder to discern, or it may be resumed too late, when blood levels have dropped substantially and when antipsychotic protection has substantially waned. Another limitation is that this approach requires frequent assessments, which may not be convenient or feasible in an outpatient setting.

The latter limitation may be overcome by allowing the patient to make an at-home decision about when to resume cariprazine at the lower dose, but most psychiatrists would be uncomfortable with such an approach because it shifts the decision-making process to the former limitation and, worse, because it may result in nonadherence to treatment. When resuming medication is left to the patient's discretion, the patient may never resume.

A Pharmacokinetically Informed Stop-and-Resume Approach

The pharmacokinetics of cariprazine and its metabolites are not linear[4] but are not so nonlinear as to invalidate the discussion that follows. If the daily dose of cariprazine is 6 mg and if cariprazine is abruptly discontinued, then, by definition, the activity of the drug and its metabolites will fall by 50% after 1 half-life, that is, in about 10 days. This is where we want the new steady state to be for a 3 mg/d maintenance dose. So, if we resume cariprazine at 3 mg/d after a 10-day drug-free interval, we will be administering the correct dose to maintain the steady state at half of what it formerly was. Thus, this strategy takes 10 days and not 50 days to get to where we want the patient to be.

In a nutshell, to quickly reach steady state at half the current dose, we must stop drug administration for 1 half-life and then resume drug administration at half the current dose. The advantage of this strategy is that there is no subjectivity in decision-making about when to reintroduce the drug nor a need for repeated clinical assessments. A disadvantage is that pharmacokinetics vary widely across patients and what is perhaps appropriate for the average patient may be only an approximation for those who metabolize the drug more slowly or more quickly.

Parting Notes

The pharmacokinetically informed stop-and-resume strategy described above can be applied to all drugs that have linear pharmacokinetics. For drugs that have nonlinear pharmacokinetics, such as drugs that are stored in lipid reservoirs, using the terminal half-life[1] would offer a reasonable approximation of what to expect.

The strategy described above can also be applied to drugs that are administered in sustained- or extended-release formulations. The actual half-life of the drug will need to be used in the calculations and not the half-life related to the artificial prolongation of duration of action. For antipsychotic long-acting injections, manufacturer guidelines will need to be followed.

If we adopt the conventional approach and reduce daily dosing from 6 mg/d to 3 mg/d, it will not necessarily take 50 days for the dose-related adverse effects of cariprazine to attenuate. Consider: after 1 half-life, blood levels of a drug drop by 50%, and after 2 half-lives, they drop by a further 25%, that is, by a total of 75%.[1] So, if it takes just 2 half-lives to get to 75% of where we want the new steady state to be, it could take just 20 days for the benefits with the reduction in cariprazine dosing to 3 mg/d to become noticeable.

What if the cariprazine dose is desired to be reduced from 6 mg/d to 4.5 mg/d and not to 3 mg/d? In such an event, an approximation could be to stop the drug for about half of a half-life and to then resume.

The 2 stop-and-resume approaches described in this article are useful only for drugs (and their metabolites), such as fluoxetine, penfluridol, and cariprazine, that have long half-lives.[2] For drugs that have short to intermediate half-lives, continuing medication without interruption but at a lower dose would be only marginally disadvantageous relative to stopping and resuming treatment. Clinical judgment should be used to decide when a stop-and-resume strategy should be applied.

Akathisia can be attenuated using drugs such as propranolol, mirtazapine, and benzodiazepines.[3] This pharmacologic neutralization approach to case management was not discussed because the purpose of this article was to explain how a knowledge of pharmacokinetics can be leveraged to improve clinical practice.

Finally, how can we get patients to quickly and efficiently stabilize at a higher rather than a lower dose of medication? Using loading doses is an alternative to merely raising the dose to the target level and waiting for 5 half-lives for steady state to be attained. Loading dose strategies have been used

for various drugs ranging from valproate to long-acting antipsychotic injections. A limitation of using loading doses is that loading results in a sharp initial rise in blood levels that may not be tolerated by all patients and for all drugs. A discussion on loading dose strategies is out of the scope of this article.

Published online: November 30, 2022.

REFERENCES

1. Andrade C. The practical importance of half-life in psychopharmacology. *J Clin Psychiatry*. 2022;83(4):22f14584.
2. Andrade C. Psychotropic drugs with long half-lives: implications for drug discontinuation, occasional missed doses, dosing interval, and pregnancy planning. *J Clin Psychiatry*. 2022;83(4):22f14593.
3. Pringsheim T, Gardner D, Addington D, et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719–729.
4. Vraylar [package insert]. Actavis Pharma, Inc; 2022.