Clinical and Practical **Psychopharmacology**

Psychotropic Drugs With Long Half-Lives:
Implications for Drug Discontinuation, Occasional Missed Doses, Dosing Interval, and Pregnancy Planning

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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

The half-life of a drug is the time taken for the blood level of the drug to fall by half, provided that no more doses of the drug are administered in the intervening period. Many psychotropic drugs and their active metabolites, if any, have very long half-lives that extend for 2 days or longer. Examples are chlordiazepoxide, diazepam, fluoxetine, vortioxetine, aripiprazole, brexpiprazole, cariprazine, penfluridol, donepezil, and memantine. Other drugs with long half-lives that psychiatrists may prescribe include levothyroxine and zonisamide. Psychotropic drugs with long half-lives take long to reach steady state; this is seldom a problem. They also take long to wash out; this is an advantage because the risk of drug withdrawal or discontinuation syndromes is small, and a disadvantage if rapid washout is desired for any reason, including the experience of drug adverse effects or toxicity, or the discovery of an unplanned pregnancy. Other clinical issues related to drugs with long half-lives include the relevance of occasional missed doses, the possibility of once-weekly dosing, and the need for pregnancy planning.

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The half-life of a drug is the time taken for the blood level of the drug to fall by half, provided that no more doses of the drug are administered in the intervening period. Terms and concepts related to half-life, and the clinical importance thereof, were explained with the help of common examples in the previous article in this column.[1]

Many drugs have long half-lives. For example, the antibacterial agent oritavancin has a half-life of about 16 days, the antimalarial agent mefloquine has a half-life of 14–41 days, and the antiarrhythmic drug amiodarone has a half-life of 21–78 days[2]; whereas values stated for these drugs and for others in the rest of this article would depend on the source consulted, the variation across sources is usually modest.

Many drugs in psychiatry have long half-lives that extend for 2 days or longer; examples are listed in Table 1. These include the benzodiazepines chlordiazepoxide and diazepam, the antidepressants fluoxetine and vortioxetine, the antipsychotics aripiprazole, brexpiprazole, cariprazine, and penfluridol, and the dementia drugs donepezil and memantine. Some of these drugs have long half-lives only because of the contribution of their active metabolites. Some of these drugs have active metabolites with even longer half-lives than those of the parent drugs. These drugs are considered in turn, as are clinically important issues related to their use.

Benzodiazepines

Chlordiazepoxide and diazepam are examples of benzodiazepines with long half-lives. Chlordiazepoxide, commonly used in the treatment of alcohol withdrawal, has a half-life of only 7–28 hours; however, this is 40 hours in the elderly. Importantly, its active metabolite, demoxepam, has a half-life of 14–95 hours.[3,4] In patients with alcoholic liver disease, the half-life of the active metabolites demoxepam and desmethylchlordiazepoxide may extend to a week and beyond.[5]

In young adults, the half-life of diazepam is about 30 hours, and that of its active metabolite desmethyldiazepam is 40–56 hours.[6,7] Because both diazepam and desmethyldiazepam accumulate in adipose tissue, their elimination half-lives increase in the obese; that of diazepam is 82 hours, and that of desmethyldiazepam is 130 hours.[6] Accumulation in adipose tissue also explains the longer half-life of diazepam (86 hours) and desmethyldiazepam (80 hours) in the elderly[7]; elderly subjects have a higher fat-to-muscle ratio than young subjects.[1]

To avoid the risk of accumulation related to impaired metabolism, chlordiazepoxide and diazepam must be used in lower doses, and with caution, in patients with alcoholic liver disease; or, lorazepam may be preferred because lorazepam is metabolized by glucuronidation (a mechanism that is relatively spared in liver disease) and because lorazepam has no active metabolites.[8,9] To avoid the risk of accumulation and delayed washout related to drug and metabolite distribution in body fat, chlordiazepoxide and diazepam should be used with caution in the elderly and in those who are overweight and obese.

The long half-life of diazepam can be advantageous. Blood levels of diazepam drop slowly when the drug is discontinued, and so diazepam is less likely to be associated with a withdrawal syndrome relative to benzodiazepines that have short half-lives. For this reason, diazepam can be substituted for short-acting benzodiazepines in the management of benzodiazepine dependence.[10]

As an aside, clonazepam, which has a half-life of about 30–40 hours, is also a long-acting benzodiazepine. However, clonazepam is not discussed in this article because its half-life is < 2 days and because it has no active metabolites that prolong its duration of action. Clonazepam is also not distributed in body fat as is diazepam. If these seem like advantages for clonazepam over chlordiazepoxide and diazepam, indeed they are, explaining why clonazepam is more widely prescribed.

Antidepressant Drugs

Fluoxetine and vortioxetine are examples of antidepressants with long half-lives. The half-life of fluoxetine is 1–3 days, and that of its active metabolite norfluoxetine is 7–15 days.[11,12] The half-life of fluoxetine may increase during maintenance therapy because fluoxetine inhibits its own metabolism,[13] and this autoinhibition may be more pronounced with higher doses of fluoxetine,[14] such as are used in the treatment of obsessive-compulsive disorder. The half-life of fluoxetine more than doubles in cytochrome P450 (CYP2D6) poor metabolizers.[15]

The half-life of vortioxetine is 57–66 hours.[16,17] The metabolites of vortioxetine are not biologically active. Exposure to vortioxetine increases in CYP2D6 poor metabolizers.

Most antidepressants have a half-life of about a day or less and so need to be gradually tapered and withdrawn lest the patient experience an antidepressant discontinuation syndrome.[18] Because fluoxetine and vortioxetine have long half-lives, washout of these drugs takes about 2 weeks (vortioxetine) to 4–5 weeks (fluoxetine and norfluoxetine), and the risk of a drug discontinuation syndrome with these drugs is therefore low.[19–22] For this reason, treatment of the selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome can be effected by substituting fluoxetine for the SSRI that is responsible for the discontinuation symptoms[23,24]; however, not all authors agree with this approach.[25]

As an aside, whereas antidepressant discontinuation symptoms are most commonly seen in the context of shorter drug half-lives, they may also be independent of drug half-life, and occur despite gradual taper and discontinuation, in patients who are exquisitely sensitive to drug discontinuation.

Antipsychotic Drugs

Aripiprazole, brexpiprazole, cariprazine, and penfluridol are examples of antipsychotic drugs with long half-lives. The mean elimination half-life of aripiprazole is about 75 hours, and that of its active metabolite, dehydroaripiprazole, is 94 hours.[26] The half-life of aripiprazole extends to 146 hours in CYP2D6 poor metabolizers.[27] The pharmacokinetics of dehydroaripiprazole are not affected by CYP2D6 inhibition[28] and so would not be expected to vary with CYP2D6 metabolic status.

The terminal half-life of brexpiprazole is 91 hours; its major metabolite, DM-3411, does not contribute to the therapeutic effects of the parent drug. The half-life of brexpiprazole in CYP2D6 poor metabolizers is not known but is expected to be prolonged, which is why dosing in poor metabolizers is recommended to be halved.[29]

Cariprazine has a half-life of 2–4 days. Its active metabolites desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR) are pharmacologically equipotent to cariprazine and have half-lives of 1–2 days and 1–3 weeks, respectively; time to steady state (and so, presumably, also time to washout) is 4–8 weeks, but may be > 12 weeks in some patients.[30]

Penfluridol is a first-generation antipsychotic that is available in some but not all parts of the world. Penfluridol has a half-life of 66 hours.[31] However, the drug is strongly lipophilic, and so is deposited in fat reservoirs in the body and brain. It is gradually released from these reservoirs, resulting in an effective prolongation of its duration of action[32]; its terminal plasma half-life is 199 hours.[33] Thus, penfluridol is, to all purposes, an orally administered depot neuroleptic that can be and is dosed once weekly.[32]

Penfluridol is extensively metabolized to (probably) inactive metabolites. There are wide variations across individuals in steady state levels and plasma elimination half-lives[32,33]; this variation is almost certainly related to variation in adiposity across individuals.

Other Drugs Used in Psychiatry

The dementia drugs donepezil and memantine have half-lives of about 70 hours each.[34] Donepezil[34] but not memantine[35] has active metabolites.

Hypothyroidism, and especially subclinical hypothyroidism, are common in depression,[36] including adolescent depression[37] and refractory depression,[38] and lithium-induced subclinical hypothyroidism has been known for long.[39] Levothyroxine, therefore, may be prescribed by psychiatrists. Levothyroxine has a long half-life of about 7 days.[40]

Zonisamide has an uncertain role in psychiatry. It has been trialled with mixed results in patients with bipolar disorder, eating disorders, and weight gain related to psychotropic medications.[41,42] The half-life of zonisamide is about 60 hours.[43]

Long-Acting Formulations and "Hit and Run" Drugs

As a reminder from the previous article in this column,[1] drugs with a long half-life have a long duration of action, but drugs with a long duration of action do not necessarily have a long half-life. Thus, orally administered drugs in delayed-release formulations have a longer duration of action only because the rate of absorption is delayed; the half-life of the drug is no different from that in immediate-release

formulations. Similarly, the prolonged action of long-acting injection (LAI) antipsychotic drugs is only because of slow release of the active drug into blood; again, the half-life of the drug is no different from that in other formulations.

Drugs can have a long duration of action for other reasons, too, such as irreversible action at the target site. As an example, because classical monoamine oxidase inhibitors (MAOIs) such as tranylcypromine irreversibly inhibit monoamine oxidase (MAO) enzymes, their duration of action lasts for as long as it takes the body to synthesize adequate levels of new MAO enzyme after the MAOI has been withdrawn; this is usually about 2 weeks. Such drugs are sometimes called "hit and run" drugs; they hit their target and then disappear from circulation—their job is done.[44] Similar considerations apply to disulfiram, or more likely to its active metabolites; these have short half-lives but irreversibly inhibit the aldehyde dehydrogenase enzymes, requiring synthesis of new enzyme for recovery of the ability to break down acetaldehyde.[45]

Clinical Importance of Long Half-Life

Drugs with long half-lives take a long time to reach steady state. This is usually of little consequence in psychiatry because time to onset of clinical benefit is usually independent of the half-life of psychotropic drugs. Anyway, as in the case of the LAIs, if higher levels are required from the outset, a loading dose strategy can be employed, or the initial interdose intervals can be shortened.[1]

Drugs with long half-lives take longer to attain washout. This can be advantageous because such drugs are less likely to be associated with drug discontinuation or withdrawal syndromes, as discussed for benzodiazepines and antidepressants in earlier sections of this article. A long half-life can be disadvantageous if rapid washout is desired for any reason, including the experience of adverse effects or toxicity. A long half-life can have other implications, as well, and these are considered in the next sections with cariprazine as a candidate drug. Readers may note that the discussion applies to other drugs with long half-lives, as well.

As already stated, the half-life of cariprazine is 2–4 days. Its active metabolites DCAR and DDCAR have half-lives of 1–2 days and 1–3 weeks, respectively.[30] Because cariprazine and these metabolites are equipotent, it could take weeks to months for the drug to reach steady state after treatment initiation (however, this does not delay the onset of efficacy, as evident from the results of randomized controlled trials [RCTs]), and weeks to months for the drug to be washed out, if discontinued. Three questions arise in this context: (1) Do occasional missed doses matter? (2) Can the dosing interval be increased? (3) What are the implications for pregnancy planning? Each of these questions is considered in turn.

Cariprazine: Do Occasional Missed Doses Matter?

The long half-lives of cariprazine and its metabolites DCAR and DDCAR, considered along with the equipotency of the parent drug and its metabolites, suggest that (1) blood levels will not fluctuate appreciably across once-daily dosing intervals and that this is likely to be true even if patients occasionally miss doses; and (2) biological activity will not fluctuate appreciably across once-daily dosing intervals and that this is also likely to be true even if patients occasionally miss doses.

From the above, it may be supposed that if patients receiving cariprazine occasionally miss doses, treatment efficacy will not be compromised. However, there is no evidence to support this speculation. Missed doses result in decreased exposure to the drug, and many missed doses result in a lower average dose. Because efficacy of drugs is usually dose-related, whereas occasional missed doses may not matter, frequent missed doses that translate into lower average doses can result in treatment failure.

The bottom line is that whether or not missed doses matter depends on how many doses are missed, regardless of the half-life and biological activity of the drug and its metabolites. However, a saving grace is that when the half-life is long, should the patient stop taking the drug for any reason, the duration of protection against relapse would be longer because of the longer persistence of the drug in the body; this conjecture is based on extrapolation from an LAI RCT.[46] There would therefore be a wider window of opportunity to resume maintenance therapy. Cariprazine and penfluridol, with their very long half-lives, could be particularly advantageous in such situations.

As an aside, some psychiatrists believe that because patients in RCTs are deemed to be adherent to treatment if they take at least 80%–90% of the treatment doses (the definition varies across RCTs), patients in clinical practice can miss up to 10%–20% of their doses without risking loss of treatment efficacy. This is a dangerous belief because no pharmaceutical company has published efficacy data based on the extent of medication adherence. The interpretation of medication adherence in RCTs is further complicated by the protective environment in which RCTs are conducted (which differs from naturalistic practice) and by the inclusion of treatment dropouts, comprising patients who completely stop taking drugs, in intent-to-treat analyses.

Cariprazine: Can the Dosing Interval Be Increased?

When treatments have long half-lives, the dosing interval can be increased. As examples, fluoxetine[47] and penfluridol[32] can both be dosed once weekly. So, can cariprazine also be dosed once weekly? The answer, for 2 reasons, is perhaps not. First, cariprazine is dosed at lower levels for bipolar depression (1.5–3.0 mg/d) and at higher levels for mania (3-6 mg/d); so, if the drug is dosed at high levels once weekly, blood levels could be too high for bipolar depression for about half the week. Thus, once-weekly cariprazine dosing may not be suitable for bipolar depression. Second, if a patient with mania or schizophrenia requires a daily dose of 6 mg for efficacy, assuming linear pharmacokinetics, the weekly dose could need to be in the region of 42 mg. At this dose, the spike in blood levels per dosing occasion

would be considerably higher than that with daily dosing; in consequence, adverse effects associated with spikes per dosing occasion could be substantial and could compromise treatment acceptability. The only way of knowing for certain, though, would be for the necessary pharmacokinetic studies and RCTs to be conducted.

Cariprazine: Does the Long Half-Life Have Implications for Pregnancy Planning?

There are no clinical data to support or refute the safety of cariprazine in pregnancy. However, preclinical studies, conducted in cell cultures and in rodent models, find that cariprazine inhibits sterol synthesis; this decreases cholesterol availability in developing neurons and in glial cells that synthesize their own cholesterol, and this also increases levels of cholesterol precursors that can be developmentally toxic to the fetus. Cariprazine is not alone in this effect; 2 other psychotropic drugs with long half-lives (aripiprazole, fluoxetine) have been shown to exhibit similar action, as have psychotropic drugs with shorter half-lives (haloperidol, sertraline, trazodone).[48–50] All of these drugs cross the placental barrier as well as the blood-brain barrier. Until more data are available, it could therefore be reasonable to want to avoid in women of childbearing potential medications such as cariprazine that have not been systematically studied in human pregnancy, unless other clinical options with better-established reproductive safety have not been adequate for the patient.

It can take 5–10 weeks (longer, in some) for cariprazine and its metabolites to be washed out of the body after drug discontinuation. So, if a woman wishes to conceive and does not want her pregnancy to be exposed to cariprazine, she must discontinue treatment at least 10–12 weeks before conception. This also means that if a woman receiving cariprazine unexpectedly discovers that she is pregnant, it is perhaps too late to stop cariprazine because her pregnancy has already been exposed to the drug until that date, and because her pregnancy will continue to be exposed to the drug and its metabolites for the next 5–10 weeks or longer; that is, well beyond the first trimester for many women. Given these considerations, it may be prudent to discuss pregnancy planning in women of childbearing age at the time of initiation of cariprazine, itself.

As an aside, unplanned pregnancy is a frequent occurrence, and many women realize that they are pregnant only after they are well into their first trimester. Therefore, reproductive planning should be automatic when prescribing to all women of childbearing age, regardless of the half-life of the drug.

Concluding Notes

This article and the previous article in this column[1] emphasize that, in order to improve psychopharmacologic skills, psychiatrists need to know the half-lives of the drugs that they prescribe as well as the half-lives of the active metabolites of these drugs.

On a parting note, not all the issues discussed in this article are issues for all the drugs. As an example, with regard to levothyroxine replacement therapy, reassessment of thyroid function tests and of the need for dose adjustment require to be done once in 5 half-lives; that is, after about 5 weeks, when steady state would have been attained.[51] This is no different from what is practiced with, say, lithium; serum lithium and the need for dose adjustment are determined after 5 half-lives, that is, after about 1 week. In contrast, in women who are hypothyroid, continuation of levothyroxine treatment through pregnancy is a necessity and not an option,[51] so the need for pregnancy planning is not the same as it is with cariprazine.

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