1 Sampling Times for Oral and Long-Acting Injectable Agents

QUICK CHECK

PRINCIPLES

- Although half-lives vary dramatically between antipsychotics, by convention levels for oral antipsychotics are obtained as 12h troughs at steady state (i.e. after five half-lives have passed for the drug of interest and a major active metabolite if also assayed). Future research may define the optimum time since last dose for each antipsychotic that best correlates with clinical outcomes.
- Half-lives also vary dramatically between long-acting injectable (LAI) antipsychotic preparations. The time to steady state may differ from that predicted by the half-life alone if the LAI is loaded at the beginning of treatment.
- By convention, levels for LAI antipsychotics are obtained at steady state 1h–72h prior to the next injection.
- Levels taken before steady state is reached or at nonstandard time intervals for oral antipsychotics (e.g. 16 hours, 24 hours) are difficult to interpret for purposes of examining drug metabolism or managing inadequate response.

INTRODUCTION

The use of antipsychotics to treat schizophrenia is fraught with many layers of complexity as prescribers try to tailor the pharmacodynamic properties of an agent to a specific patient based primarily on subjective response. Variations in drug metabolism related to genetic polymorphisms, or to medication or environmental exposures (e.g. smoking), and variable adherence with oral medications lead to scenarios that confound even seasoned clinicians. Excluding the realization that up to one-third of schizophrenia patients may not respond adequately to non-clozapine antipsychotics, 60 years of antipsychotic research has demonstrated that dose is a poor correlate of response likelihood, whereas plasma drug levels represent the best ***clinically available tool*** that quantifies the relationship between drug exposure and central nervous system (CNS) activity [1]. The classic equation by psychopharmacologist Sheldon Preskorn illustrates the variables involved in clinical drug response (Figure 1.1). The typical method of antipsychotic initiation starts with "usual" doses, followed by subsequent titration until one of two hard endpoints are met: adequate clinical response or intolerable adverse effects. Given the numerous permutations outlined by Preskorn, including the fact that a major limiting factor on absorption is failure to take the prescribed dose, the common clinical approach is inefficient at best, and can lead to erroneous conclusions when patients are outliers on a dose–response curve. In a sample of 99 schizophrenia patients deemed treatment-resistant and in need of clozapine at an academically affiliated London clinic, 35% had plasma antipsychotic levels that were subtherapeutic, and, of these, 34% were undetectable [2]. As will be covered extensively in this handbook, noting that inadequate responders have lower than expected antipsychotic levels is a crucial first step in optimizing treatment, followed by a determination of whether this is due to poor adherence or kinetic factors.

Figure 1.1 Preskorn's equation for clinical drug response [1]

Clinical response	=	Drug affinity for and activity at the site of action	X	Drug concentration at the site of action*	X	Underlying patient biology**

Variables

* Absorption, distribution, metabolism, elimination

** Genetics, age, disease, environment

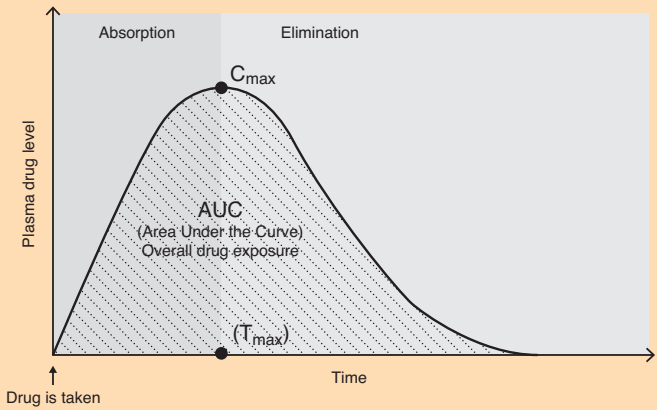
(Adapted from: S. H. Preskorn [2010]. Outliers on the dose–response curve: How to minimize this problem using therapeutic drug monitoring, an underutilized tool in psychiatry. *J Psychiatr Pract*, 16, 177–182.)

Whether tracked via plasma levels, pill counts, or medication event monitoring system (MEMS) pill bottle caps that electronically record each opening, oral antipsychotic nonadherence in schizophrenia patients is greater than 50% for short periods (e.g. four weeks), and increases over time [3, 4]. Even in the ideal situation where highly motivated individuals are 100% adherent with an oral antipsychotic, the construction of models to correlate dose and systemic levels is exceedingly difficult. One study sought to create a model of olanzapine exposure based on data acquired from paid healthy volunteers [5]. The investigators found that the following variables were needed for the final model to robustly predict olanzapine trough levels: ethnicity, gender, age, height, weight, liver and kidney function, and cytochrome P450 1A2 phenotype (as determined by the ratio of caffeine metabolites to caffeine in saliva). This model did have a correlation coefficient of 0.833 compared with observed values, but serves as a powerful reminder that any assumptions about antipsychotic levels based on dose alone are unlikely to be accurate [5].

The ability to use plasma antipsychotic levels for treatment optimization requires that clinicians understand basic kinetic principles so samples are obtained at times that are interpretable for the purposes of assessing adherence and optimizing antipsychotic response [6, 7]. In addition to differing actions at CNS receptors, antipsychotics (and any active metabolites) also have a range of kinetic properties. The extent of drug exposure over a period of time (e.g. 24 hours) is referred to as the **area under the curve, or AUC,** and this totality of exposure as measured in plasma is highly correlated with that obtained in cerebrospinal fluid [8]. Calculation of AUC as performed in pharmacokinetic (PK) studies requires multiple specimens to be obtained at frequent intervals over the time frame in question (typically 24 hours) (Figure 1.2). While AUC is the best proxy for overall CNS drug exposure, determining this value for an individual patient is impractical. However, not only is determination of a trough antipsychotic plasma level feasible in routine clinical practice, PK models have shown that this single point estimate serves as a useful proxy for AUC, and thereby for the extent of CNS exposure [9].

Given the broad range of antipsychotic half-lives, the optimal approach to this problem would involve determining the ideal time point that a single plasma level should be drawn for a specific antipsychotic at steady state to predict AUC [9]. The US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study provided a large body of real-world plasma level data that investigators have mined to model optimal sampling times. The CATIE schizophrenia trial data set contains many

Figure 1.2 Illustrated example of area under the curve

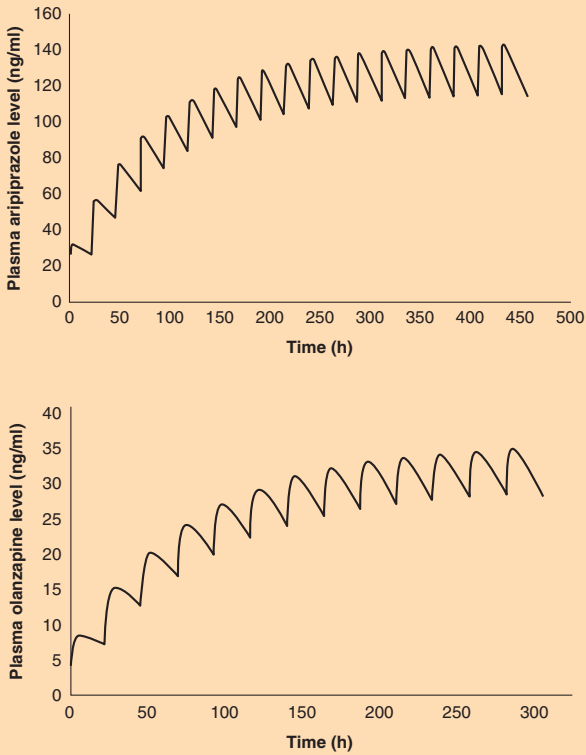


samples drawn at nonstandard times and is considered quite noisy for the purposes of data analysis, but to some extent it does represent the messiness of real-world antipsychotic usage. Figure 1.3 illustrates examples of the variations in drug levels over time for two medications with different half-lives approaching their respective steady state levels. Based on detailed analyses of the multiple antipsychotics used in CATIE, the authors concluded that collection of samples at ***three time points*** might be needed for optimal sampling of each antipsychotic medicine. The authors did acknowledge that this is a preliminary attempt to examine this problem, that the recommendation for three timed samples is not practical for clinical purposes, and that many antipsychotics contain active metabolites, so future studies must model both the parent compound and the principal active metabolites [9]. Until that time when research identifies practical methods for individual antipsychotic preparations that best correlate with AUC and CNS drug actions, the literature has focused on presenting data obtained at standard post-dose intervals for oral and long-acting injectable antipsychotics (LAIs) that represent a defined trough value at steady state: 12 hours for oral antipsychotics, and just prior to the next injection for LAIs.

A When Is Steady State Achieved?

Steady state represents the period when equilibrium has been reached in the variables that govern drug absorption, distribution, metabolism, and elimination. While some oral antipsychotics have poor bioavailability as a consequence of extensive first-pass

Figure 1.3 Time to steady for aripiprazole 30 mg/d and olanzapine 20 mg/d calculated from data in the CATIE schizophrenia trial [9]



(Adapted from: V. Perera, R. R. Bies, G. Mo, *et al.* [2014]. Optimal sampling of antipsychotic medicines: A pharmacometric approach for clinical practice. *Br J Clin Pharmacol*, 78, 800–814.)

metabolism, the portion of active drug reaching systemic circulation tends to appear quite rapidly, with the time to maximal blood levels (T_{max}) ranging from 1 to 2 hours for most agents [10]. The half-life of an oral antipsychotic (once absorbed) is mostly related to the rapidity of drug metabolism, and to a lesser extent excretion of active drug or active metabolites. The rise toward steady state can be predicted by the drug half-life, and is based on the mathematical calculation that repeated dosing allows an oral medication to reach 97% of steady state trough values after five half-lives (see Box 1.1).

Box 1.1 Why Five Half-Lives Equates to Steady State

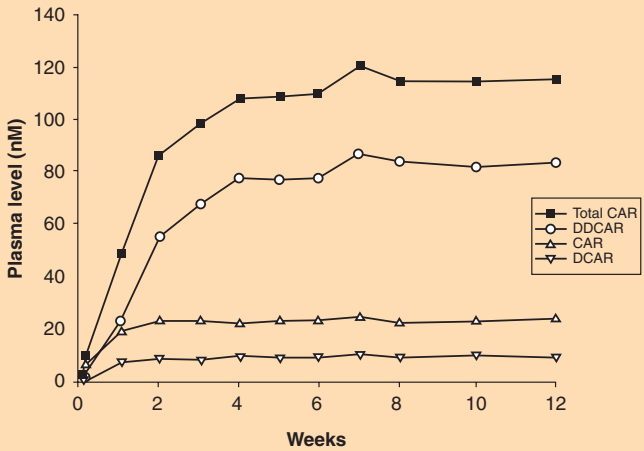
Example: Antipsychotic with a 24-hour half-life is dosed once daily. The accumulated medication levels and contribution from each dose are noted below. After five half-lives, the medication is at 97% of the steady state value.

	1st dose	2nd dose	3rd dose	4th dose	5th dose	Total
24 hours	50%	–	–	–	–	50%
48 hours	25%	50%	–	–	–	75%
72 hours	12.5%	25%	50%	–	–	87.5%
96 hours	6.25%	12.5%	25%	50%	–	93.75%
120 hours	3.125%	6.25%	12.5%	25%	50%	96.875%

Obtaining a plasma level before steady state is reached may lead to erroneous conclusions about adherence or drug metabolism, so clinicians should have a working knowledge of half-lives for commonly used antipsychotics, and for important active metabolites such as 9-OH risperidone and norclozapine, whose levels are typically provided along with the parent compound concentration (Table 1.1). The majority of antipsychotics have half-lives under 34 hours, meaning that steady state will be achieved within a week of drug initiation or a dose increase [7]. The important exceptions include sertindole (60–73 hours), aripiprazole (75 hours), brexpiprazole (91 hours), and cariprazine (31.6–68.4 hours, with active metabolites desmethylcariprazine [DCAR] 29.7–39.5 hours, and didesmethylcariprazine [DDCAR] 314–446 hours). As seen in Figure 1.4, the extremely long half-life of DDCAR means that steady state for the active moiety (i.e. the combination of drug levels for cariprazine and its active metabolites) may not be achieved for 30 days or longer [11]. As of this writing, no commercial laboratory is offering cariprazine assays, but should these be available they may be difficult to assess if DCAR and DDCAR levels are not provided, and if the level is obtained before all components of the active moiety are at steady state.

While there are antipsychotics with half-lives significantly less than 24 hours (e.g. clozapine, molindone, risperidone, ziprasidone), most appear effective in routine clinical practice with once daily dosing, with compelling evidence that tolerability across all antipsychotics is improved when that daily dose is administered at bedtime [13, 14]. For clozapine and risperidone, the formation of active metabolites with longer half-lives provides a rationale for efficacy with q 24 hour dosing, while molindone appears not to have active metabolites and remains a bit of a mystery since clinical trials indicate persistent effectiveness with once daily dosing [15]. The ziprasidone package insert advises twice daily (BID) dosing with 500 kcal food, but ziprasidone administered once

Figure 1.4 Oral cariprazine kinetics [12]



(Adapted from: Allergan USA Inc. [2019]. Vraylar package insert. Madison, NJ.)

daily has been studied. In a long-term double-blind randomized trial using haloperidol as an active comparator, ziprasidone 80–120 mg once daily appeared as efficacious as 40–80 mg given twice daily, based on discontinuation rates: 65% for ziprasidone BID vs. 58% for ziprasidone qD [16]. The proportion who attained at least one period of symptomatic remission (during the 40-week initial period and 156-week blinded continuation study) was 57% for ziprasidone in either the BID or qD group, compared to 45% for haloperidol, a difference that was not statistically significant. As will be discussed in Section B below, in those uncommon instances where BID dosing is necessary (e.g. a clozapine-treated patient who has reached their maximum tolerated bedtime [QHS] dose; a ziprasidone patient who does better with BID dosing), the bulk of the dose should be given as close to bedtime as possible so that the 12h trough level will not be distorted by having a large proportion of the medication (e.g. 50%) administered 24 hours previously.

Box 1.2 Why Oral Antipsychotics Should Be Dosed Predominantly at Night

a It is difficult to interpret plasma levels drawn on samples obtained 24 hours after a dose (as seen with qam dosing, or with twice daily dosing where half of the dose will have been administered 24 hours before the plasma level is obtained)

Rationale:

i The majority of studies examining correlations between oral and trough plasma levels are based on 12h post-dose data.

ii The majority of data examining the correlation between plasma antipsychotic levels and response is based on 12h post-dose data.

b There is no therapeutic advantage to multiple daily dosing. In those uncommon instances where BID dosing is necessary (e.g. a clozapine-treated patient who has reached their maximum tolerated bedtime dose; a ziprasidone patient who does better with BID dosing), the bulk of the dose should be given as close to bedtime as possible so that the 12h trough level will not be distorted by having a large proportion of the medication (e.g. 50%) administered 24 hours previously.

Rationale:

i Despite short peripheral half-lives, most antipsychotics have central nervous system (CNS) half-lives and effects that persist ≥ 24 hours, so once daily dosing is sufficient. Clozapine is the best cited example, and exhibits no demonstrable loss of efficacy when dosed exclusively at bedtime [13, 17]. Molindone has a half-life of 2 hours, but is also effective with once daily dosing [18].

ii There is compelling evidence that evening dosing improves tolerability, as peak CNS levels that might exceed the tolerability threshold are achieved during sleep. The best illustration of this concept is seen in the clinical trials of lurasidone. Initial adult schizophrenia studies were performed with morning dosing: "Study medication was administered in the morning with a meal or within 30 minutes after eating" [19]. Later studies administered medication with an evening meal, and analyses of adverse effects found that somnolence and akathisia were markedly reduced with evening meal dosing. In particular, the 160 mg dose had an akathisia rate when dosed with an evening meal of 6.5%, less than one-third that seen with 120 mg when given in the morning (20.3%) [20, 14].

Table Morning-meal versus evening-meal dosing: placebo subtracted rates of somnolence and akathisia in short-term adult schizophrenia trials with lurasidone [14]

	40 mg	80 mg	120 mg	160 mg
Akathisia – AM meal	7.1%	9.1%	20.3%	Not studied
Akathisia – PM meal	2.3%*	8.7%	Not studied	6.5%
Somnolence – AM meal	3.6%	4.9%	9.3%	Not studied
Somnolence – PM meal	2.8%	0.2%*	Not studied	5.8%

* Not significantly different from placebo.

Table 1.1 Mean half-life of commonly used oral antipsychotics and important metabolites [21–29, 10, 15, 17, 30, 7]

Drug	$T_{1/2}$ (hours)
First-generation antipsychotics	
Chlorpromazine	11.05–15
Fluphenazine	13
Haloperidol	24
Loxapine 7-OH loxapine	4 ??[a]
Molindone	2[b]
Perphenazine	9–12
Zuclopenthixol	17.6
Newer antipsychotics	
Amisulpride	12
Aripiprazole	75
Asenapine sublingual Asenapine transdermal patch	24 30[c]
Brexpiprazole	91
Cariprazine Desmethylcariprazine (DCAR) Didesmethylcariprazine (DDCAR)	31.6–68.4 29.7–39.5 (DCAR) 314–446 (DDCAR)
Clozapine Norclozapine	9–17 20
Iloperidone	15–22
Lumateperone	18
Lurasidone	28.8–37.4[d]
Olanzapine	30
Paliperidone (9-OH risperidone)[e]	23
Quetiapine Norquetiapine	7 12
Risperidone Paliperidone (9-OH risperidone)[f]	3 21

Drug	$T_{1/2}$ (hours)
Sertindole	60–73
Ziprasidone	7

Comment
Half-lives may be markedly prolonged in individuals receiving metabolic inhibitors or who have lower-functioning polymorphisms of cytochrome P450 enzymes, other relevant enzymes, or transporters involved in drug disposition. Conversely, half-lives may be significantly shorter than the mean in individuals exposed to inducers, or who have higher-functioning polymorphisms of cytochrome P450 enzymes, other relevant enzymes, or transporters involved in drug disposition.

[a] Based on studies of inhaled loxapine, the half-life of 7-OH loxapine is likely to be substantially longer [31].
[b] The therapeutic effects persist for 24–36 hours despite the absence of active metabolites [13].
[c] After patch removal.
[d] Repeated dosing in adult schizophrenia patients. Single dose half-life in volunteers is 18 hours [32].
[e] When administered as oral paliperidone.
[f] When derived from orally administered risperidone.

While the half-life of oral antipsychotics is based on how quickly one can eliminate the drug via metabolism and excretion, that for LAIs relates to the rate of drug absorption from the injection site.

To create an LAI medication, one must develop a prodrug or technology (e.g. embedded microspheres, polymer gel solution) that limits absorption into systemic circulation so delivery occurs in a slow, predictable manner [33, 34]. It is the time course of absorption, or absorption half-life, that becomes the determining factor of drug exposure following each injection, not the metabolism of the absorbed drug. For example, haloperidol has a half-life of 18 hours when administered intravenously [35], but the decanoate LAI preparation has a half-life of 21 days [36]. The term for this phenomenon is 'flip-flop kinetics' as the LAI half-life has been flipped on its head, so to speak, and no longer bears any relation to the drug itself but only that of the delivery system [36, 37]. Due to the systemic delivery, the antipsychotic enters tissue compartments more readily than with oral administration making the calculation of half-lives dependent on complex models of multicompartment kinetics, often with biphasic elimination curves [38, 39]. An underlying concept is that partitioning into tissue compartments eventually slows down as tissue sites reach a point of saturation. When that occurs, increased systemic drug levels are seen and a state of equilibrium is finally achieved [38].

Despite the more complicated kinetics of LAIs, clinicians can use half-life estimates to obtain an approximate calculation of when steady state might be achieved (Table 1.2), with the caveat that steady state might be achieved sooner than

Table 1.2 Mean half-life and kinetic properties of commonly used long-acting injectable (LAI) antipsychotics [45–48]

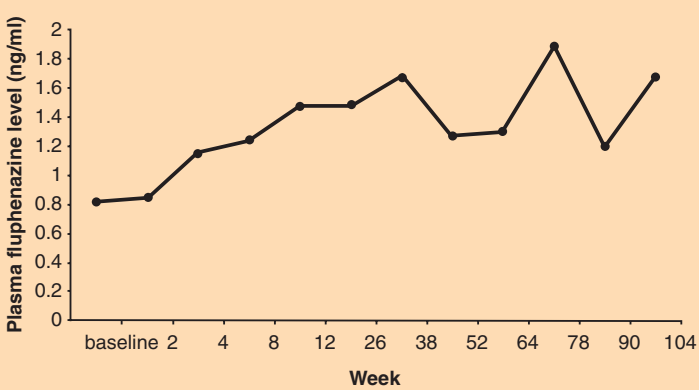
Drug	Vehicle	Dosage	T_{max}	$T_{1/2}$ multiple dosing	Able to be loaded
First-generation antipsychotics					
Fluphenazine decanoate	Sesame Oil	12.5–75 mg/2 weeks **Max:** 75 mg/ week	0.3–1.5 days	14 days	Yes
Haloperidol decanoate	Sesame Oil	25–300 mg/4 weeks **Max:** 300 mg/2 weeks	3–9 days	21 days	Yes
Perphenazine decanoate	Sesame Oil	27–216 mg/3–4 weeks **Max:** 216 mg/3 weeks	7 days	27 days	Yes
Flupenthixol decanoate	Coconut Oil	20–40 mg/2–4 weeks **Max:** 100 mg/2 weeks	4–7 days	17 days	Yes
Zuclopenthixol decanoate	Coconut Oil	25–100 mg/2–4 weeks **Max:** 400 mg/2 weeks	3–7 days	19 days	Yes
Newer antipsychotics					
Risperidone subcutaneous **(Perseris®)**	Water	90–120 mg/4 weeks **Max:** 120 mg/4 weeks	7–8 days	9–11 days	Not needed
Risperidone microspheres **(Risperdal Consta®)**	Water	12.5 – 50 mg/2 weeks **Max:** 50 mg/2 weeks	21 days	See note [a]	**No** (21–28 days oral overlap)
Paliperidone palmitate **(Invega Sustenna®)**[b]	Water	39–234 mg/4 weeks (25–150 mg/4 weeks) **Max:** 234 mg/4 weeks (150 mg/4 weeks)	13 days	25–49 days	Yes

Drug	Vehicle	Dosage	T_{max}	$T_{1/2}$ multiple dosing	Able to be loaded
Paliperidone palmitate (3 mo) (Invega Trinza®)[c]	Water	273–819 mg/12 weeks (175–525 mg/12 weeks) **Max:** 819 mg/12 weeks (525 mg/12 weeks)	84–95 days (deltoid) 118–139 days (gluteal)	30–33 days	**No**
Olanzapine pamoate (Zyprexa Relprevv®)	Water	150–300 mg/2 weeks 300–405 mg/4 weeks **Max:** 300 mg/2 weeks	7 days	30 days	Yes
Aripiprazole monohydrate (Abilify Maintena®)	Water	300–400 mg/4 weeks **Max:** 400 mg/4 weeks	6.5–7.1 days	29.9–46.5 days	**No** (14 days oral overlap)
Aripiprazole lauroxil (Aristada®)[d]	Water	441 mg, 662 mg, 882 mg/4 wks 882 mg/6 weeks 1064 mg/8 weeks **Max:** 882 mg/4 weeks	41 days (single dose) [49] 24.4–35.2 days (repeated dosing) [50]	53.9–57.2 days	No (Start with AL_{NC} 675 mg IM + 30 mg oral ***OR*** 21 days oral overlap)
Aripiprazole lauroxil nanocrystal (Aristada Initio®)[e]	Water	675 mg once	27 days (range: 16 to 35 days)	15–18 days (single dose)	–

[a] Steady state plasma levels after 5 biweekly injections are maintained for 4–5 weeks, but decrease rapidly at that point with a mean half-life of 4–6 days [51].
[b] The dosages in parentheses reflect those used outside the US, expressed as paliperidone equivalent doses.
[c] Only for those on paliperidone palmitate monthly for 4 months. Cannot be converted from oral medication.
[d] Requires 21 days oral overlap unless starting with aripiprazole lauroxil nanocrystal (AL_{NC}) + a single 30 mg oral dose.
[e] Aripiprazole lauroxil nanocrystal (AL_{NC}) is only used for initiation of treatment with aripiprazole lauroxil, or for resumption of treatment. It is always administered together with the clinician-determined dose of aripiprazole lauroxil, although the latter can be given ≤ 10 days after the aripiprazole lauroxil nanocrystal injection.

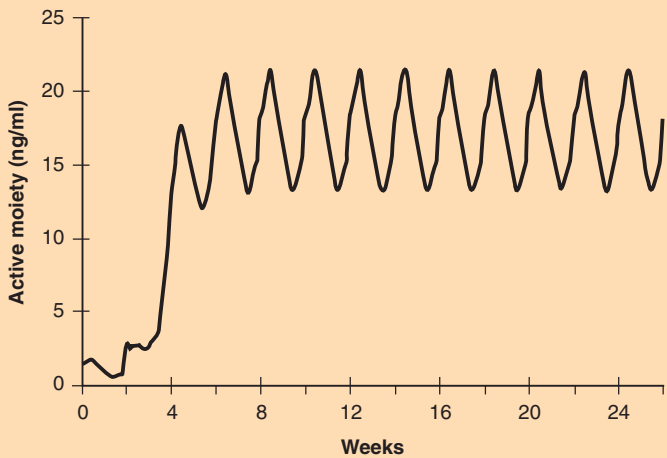
predicted if the LAI is loaded at the onset of treatment. Sadly, the data provided in LAI package inserts may not provide an accurate picture of the kinetic picture and time to steady state [40]. Visual illustrations of LAI plasma levels over time are very helpful in deciding when an LAI is at steady state and a trough plasma level can be obtained [41]. (Whenever possible, such graphic representations of LAI kinetics will be provided in this volume in the respective chapters covering a particular antipsychotic.) Figure 1.5 is one example of an expected slow rise to steady state plasma levels over 4–6 months, in this case for fluphenazine decanoate 25 mg administered every 2 weeks (q 14 d) [42]. Risperidone microspheres have an unusual kinetic profile and the package insert lists a half-life of 3–6 days for the active moiety (risperidone + 9-OH risperidone) mostly due to the delayed erosion of the microspheres and relatively sharp rise and decay in drug levels [43]. As noted in Figure 1.6, steady state levels, in practice, are not seen in the expected five half-lives predicted by the package insert (i.e. 15–30 days), but after 6 weeks of treatment with q 14 d injections [44, 40]. In general, the basic principle noted in Box 1.1 for oral antipsychotics holds for LAIs: with repeated dosing there is a steady accumulation of medication over time until an equilibrium level is reached. Figure 1.7 illustrates this concept from a kinetic modeling study of LAI olanzapine covering 1 year of treatment with monthly injections [37].

Figure 1.5 Time to steady state for fluphenazine decanoate 25 mg every 2 weeks when resuming treatment after holding injections for 4 weeks [42]



(Adapted from: S. R. Marder, K. K. Midha, T. Van Putten, *et al*. [1991]. Plasma levels of fluphenazine in patients receiving fluphenazine decanoate: Relationship to clinical response. *Br J Psychiatry*, 158, 658–665.)

Figure 1.6 Model of active moiety levels (risperidone + 9-OH risperidone) from risperidone microsphere 25 mg IM every 2 weeks with no bridging oral therapy [44]

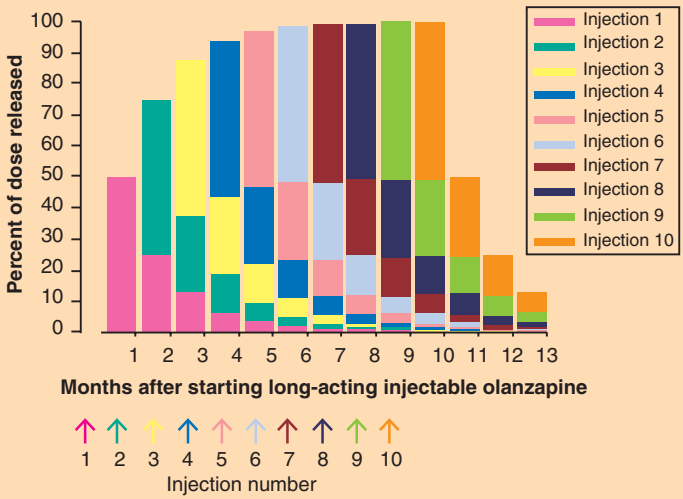


(Adapted from: W. H. Wilson [2004]. A visual guide to expected blood levels of long-acting injectable risperidone in clinical practice. *J Psychiatr Pract*, 10, 393–401.)

B Sampling Times for Oral and Long-Acting Injectable Antipsychotics

Half-lives of oral antipsychotics can be estimated accurately for groups of individuals who are not taking medications that alter drug metabolism or excretion, or who lack genetic variants that influence these processes; however, there is marked interindividual variation from the mean half-life in real-world practice. Moreover, the early literature correlating use of plasma antipsychotic levels and clinical outcomes (efficacy and tolerability) reported data from a variety of time points from 2h to 24h post-dose, making comparisons between studies difficult [52, 53]. As the literature evolved through the late 1970s, investigators settled on the use of a 12h trough for oral antipsychotics and most other psychotropic medications [54]. This decision represents a compromise that favors feasibility. The nadir plasma level for any oral medication given once daily is 24h post-dose, but obtaining plasma levels at 9 PM or 10 PM for patients who take medication at bedtime is not possible for the majority of outpatients, and at times can be challenging on inpatient psychiatric units that do not have round-the-clock

Figure 1.7 Contribution of individual injections to steady state levels for olanzapine LAI [37]



(Adapted from: S. Heres, S. Kraemer, R. F. Bergstrom, *et al*. [2014]. Pharmacokinetics of olanzapine long-acting injection: the clinical perspective. *Int Clin Psychopharmacol*, 29, 299–312.)

phlebotomy services. There are also no compelling data to suggest that plasma levels obtained at time points other than 12h are better at predicting outcomes [55]. The convergence of the literature toward measurement of 12h trough levels thus provides a time interval for a level between 8 AM and 10 AM that is practical for hospital settings, less inconvenient for outpatients, and easily reproduced across studies.

One important use of plasma antipsychotic levels is to optimize treatment efficacy and minimize adverse effect burden, but the other crucial value in level measurement is to track adherence and determine whether low levels are the product of ultrarapid metabolism [2]. The bulk of modern data correlates dose and plasma levels based on 12h trough values, so clinicians can readily find the expected level based on a given dose, assuming the level was drawn approximately 12±2h after the dose. When the level is obtained more than 2h from the 12h mark, interpretation becomes difficult as it may be impossible to find the expected level for an 8h or 16h trough. However, levels drawn at nonstandard times can be used to monitor adherence if the same time

since last dose is observed. An example would be a patient who can only obtain levels as 16h troughs (e.g. at noon) as they do not wish to miss their part-time morning employment. In an adherent individual, the expectation is that the level would fluctuate no more than 30% between determinations [56]. (See Chapter 4 for further discussion on levels and adherence.)

As noted previously, there is no compelling evidence that antipsychotic efficacy is increased with BID dosing. Many medications with short peripheral half-lives, such as clozapine, are commonly dosed on a QHS schedule [13]. There will be instances when some portion of the antipsychotic dose cannot be given in the evening, but clinicians should keep the largest fraction of the dose at bedtime. As noted in Box 1.3, when a drug with a 24h half-life is evenly divided in BID doses, the level obtained the next day will be at least 20% lower than expected, as it represents a 12h trough for half of the drug dose, and a 24h trough for the other half.

For LAIs, the trough levels at steady state occur just prior to the next injection. Ideally, one would draw the plasma antipsychotic level in the clinic just prior to administering the next LAI injection; however, some clinics do not have an on-site phlebotomy service, and the level must be drawn at an outside laboratory. As a matter of practicality, a trough LAI level can be obtained any time from 1h to 72h before the next dose. The time to steady state for an LAI will depend on whether there is a loading or initiation regimen, so clinicians must know if the level obtained is indeed at steady state, or is drawn at other relevant time points (i.e. after a loading regimen) to ascertain the extent of systemic antipsychotic exposure [57]. It is crucial that one avoids obtaining steady state trough levels at times that are too close to the maximum

Box 1.3 How Trough Levels Are Influenced by Dosing Interval: An Example from Lithium

Like many antipsychotics, lithium has a 24-hour half-life, but older literature recommended split daily dosing [58]. Below are trough plasma levels obtained 12 hours after the evening dose at steady state in patients on identical daily doses administered one of two ways: all at bedtime (QHS) or twice daily (BID). The levels obtained on BID dosing are 22% lower than those with QHS dosing.

	Level on QHS dosing	BID dosing
Amdisen 1977 [59]	1.37 mEq/L	1.07 mEq/L
Greil 1981 [60]	1.04 mEq/L	0.81 mEq/L
Swartz [61]	0.90 mEq/L	0.70 mEq/L
Mean	**1.10** mEq/L	**0.86** mEq/L

plasma concentration (T_{max}) of the LAI preparation. In general, a plasma level drawn 1h–72h before the next LAI dose avoids these issues, even for agents with short injection intervals (e.g. fluphenazine decanoate, risperidone microspheres).

Box 1.4 Basic Guidelines for Obtaining Trough Antipsychotic Plasma Levels

a Oral antipsychotics

- **i** Trough levels should be drawn at steady state. This is reached after five half-lives from initiation or after a dose increase, and should factor in the half-life of active metabolites that are often reported (e.g. 9-OH risperidone, norclozapine).
- **ii** By convention, trough levels are drawn 12h post-dose [7]. There is no compelling efficacy reason to routinely divide antipsychotic doses throughout the day, and bedtime dosing improves tolerability [14]. Even clozapine is usually administered all at bedtime despite the short peripheral half-life [13]. In instances where the dose must be divided, the bulk of the dose should be given at bedtime. If evenly split into qam and QHS doses, the trough level drawn the next morning will be 20% lower for a medication with a 24h half-life, as half of the dose was administered 24h before the level was drawn.
- **iii** Levels drawn at nonstandard times (e.g. 16h post-dose) may be difficult to interpret. If obtained consistently at that time, the level could be used to track adherence based on the assumption that it should not vary by more than ± 30% if drawn at the same time interval post-dose (± 2h) (see Chapter 4) [17].

b LAI antipsychotics

- **i** Trough levels should be drawn at steady state. This may not be exactly after five half-lives from initiation due to the more complex kinetics of LAI preparations, and whether a loading regimen was used. Clinicians should be familiar with the kinetic profiles of LAIs that they use frequently, and the plasma level and kinetic profiles of LAIs that can be loaded or have an initiation regimen.
- **ii** The trough level is typically obtained 1h–72h before the next injection. Levels drawn at earlier time points run the risk that the medication level is closer to the maximum concentration than to the nadir level.

Summary Points

- **a** Whether the antipsychotic is taken orally or as a long-acting injection (LAI), trough levels must be obtained at appropriate time intervals since the last dose. By convention this is 12h after oral dosing, or 1h–72h before the next LAI dose.
- **b** Clinicians should be familiar with the half-lives of commonly used oral antipsychotics and understand that steady state is reached after five half-lives

of the medication, including those of active metabolites. Levels of two active metabolites are frequently reported by laboratories: 9-OH risperidone and norclozapine.

c Steady state for LAI preparations is governed by what is termed flip-flop kinetics: the half-life is primarily related to the rate of drug absorption (i.e. the delivery-system kinetics) and not to the molecule that is being delivered. The time to steady state may vary from the rule of five half-lives due to the complexities of systemically delivered drug distribution, and whether the LAI was loaded. Clinicians should be familiar with the kinetic profiles of commonly used LAI agents under both circumstances (loading and non-loading).

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