Psychopharmacology (1989) 98:433–439

Psychopharmacology
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Review

Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications

Stephen R. Marder[1], John W. Hubbard[2], Theodore Van Putten[1], and Kamal K. Midha[2]

[1] West Los Angeles Veterans Administration Medical Center, Brentwood Division and the School of Medicine, University of California, Los Angeles, CA 90073, USA

[2] Colleges of Pharmacy and Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7NOWO

Abstract. The authors review the literature regarding the pharmacokinetics of long-acting injectable neuroleptic drugs (LINS). There are important differences between LINS and oral neuroleptics that affect their pharmacokinetics. By avoiding first pass metabolism in gut and liver, LINS result in lower circulating concentrations of metabolites than are found after oral administration. In addition, LINS take more time to reach a stable steady state than their oral counterparts. The clinical significance of these pharmacokinetic properties is discussed. The authors recommend that when patients are being changed from oral neuroleptics to LINS, that this conversion be done gradually over several months.

Key words: Schizophrenia – Neuroleptics – Pharmacokinetics – Long-acting neuroleptics

Long-acting injectable neuroleptics (LINS) provide a method for medicating schizophrenic patients without requiring that they take pills on a regular basis. The injection is administered intramuscularly once every 1–4 weeks depending on the particular drug selected. The drug is slowly released from the injection site, providing a reasonably steady plasma level over the entire interval, a property which has led to these drugs being heavily utilized by clinicians. Indeed, some view these medications as being preferable to oral neuroleptics for the large proportion of chronic schizophrenic patients who require long-term maintenance therapy (Freeman 1980). This is because LINS provide a partial solution to the problem of noncompliance which can seriously compromise the treatment of schizophrenic patients. This advantage of depot drugs is best demonstrated in studies such as those conducted by Johnson and his coworkers (1984) under conditions that resemble most closely those that exist in community clinics. In these studies, patients with histories of poor compliance are included in the population and the amount of contact between patients and staff are limited. In the larger, more carefully controlled investigations (Hogarty et al. 1979; Schooler et al. 1980) patients with serious compliance problems – that is, the individuals most likely to benefit from treatment with LINS – are commonly not included. In addition, the amount of contact between treating staff and patient usually exceeds that available in community programs. However, a careful look at the later studies indicates that there may be advantages for LINS even under these carefully controlled conditions. In both the Schooler and Hogarty studies there were no differences in outcome between oral and depot fluphenazine at the end of 1 year. The Hogarty study also included a second year during which patients receiving fluphenazine decanoate demonstrated a lower risk of relapse than those assigned to oral fluphenazine. Moreover, the best outcomes were found for patients who received fluphenazine decanoate supplemented by a form of social therapy. These results suggest that LINS may be the preferred route of neuroleptic administration for patients who are selected for being reliable and stable and who are treated in a setting enriched with social therapies.

There are two important differences between LINS and oral neuroleptics which affect their pharmacokinetics. LINS avoid first pass metabolism in gut and liver, conceivably resulting in lower circulating concentrations of the metabolites than are found after oral administration, and LINS have longer accumulation half-lives than their oral counterparts and therefore require more time to reach a stable steady state and a longer time to disappear from plasma after the termination of treatment. These properties of LINS can also become serious problems. The prescribing clinician has less flexibility: the long time taken to achieve steady state may mean that the patient's condition may not be controlled adequately during the initial stages of treatment. Conversely, the slow disappearance of drug from plasma when therapy is stopped may be a problem if the patient experiences serious side effects. These characteristics of LINS suggest that a knowledge of their pharmacokinetics may be even more important for depot than oral drugs. This review will document the evidence supporting these differences in kinetics and will focus largely on the implications of these differences as they affect clinical practice.

Explanation of slow-release characteristics

There are two possible explanations for the slow-release characteristics of LINS. The first is that the rate of release is dependent upon the rate of hydrolysis of the esterified drug by esterases in muscle tissues or blood. The second is that the rate limiting factor is the rate of diffusion of the esterified neuroleptic from the oil vehicle. Data from animal studies indicate that the latter explanation is correct

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in dogs, there appeared to be a slow, monoexponential release of radioactivity from the depot with a half-life of 4–5 days. By contrast, in vitro experiments showed that hydrolysis of the ester group to yield clopenthixol occurred rapidly in blood and a variety of tissue preparations, including muscle. In similar experiments in dogs, Dreyfuss and coworkers (1976a) found that 18.6% of radioactivity remained at the injection site 35 days after the intramuscular injection of fluphenazine decanoate. On the other hand, after the intravenous injection of FD to dogs, thin layer chromatography showed that most of the drug in plasma was in the unesterified form, indicating rapid hydrolysis of the decanoate ester by blood esterases in vivo (Dreyfuss et al. 1976b). By contrast, experiments in which fluphenazine decanoate was incubated with plasma or tissue preparations suggested that the rate of hydrolysis in vitro was very slow. At present, it is not clear why there is a discrepancy between the apparent rates of hydrolysis of fluphenazine decanoate in vitro and in vivo.

Available long-acting injectable neuroleptics

The first available LIN was created when fluphenazine hydrochloride had its side chain esterified with heptanoic acid, producing fluphenazine enanthate (FE). The resulting molecule was not absorbed until it was hydrolyzed by muscle esterases, thus releasing free fluphenazine. Decanoic acid was used later for esterification since hydrolysis of the resulting drug, fluphenazine decanoate (FD), was somewhat slower. Both clinical experience and laboratory evidence (Dreyfuss et al. 1976a, b) have demonstrated that FD has a longer interinjection interval. Not surprisingly, it has replaced FE which is seldom used today. Currently, more than a dozen different LINS are available world-wide. This review will focus on three of the most widely used drugs. However, the emphasis will be on pharmacokinetic principles which are likely to be generalizable to any LIN.

Significance of the oil vehicle

The two oil vehicles which have been most commonly used in formulating depot neuroleptics are sesame oil and viscoleo. The characteristics of the oils are important since one of the important factors contributing to the sustained release of the neuroleptic is the oil/water partition coefficient. In one study (Knudsen et al. 1985) perphenazine decanoate was administered to two patients in both sesame oil and viscoleo. The study concluded that lower, but more even plasma concentrations of perphenazine were associated with sesame oil. Unfortunately, there are few data on the effect of the type of oil on the pharmacokinetics of LINS, probably because any given commercial depot injection is usually available as a formulation in one particular type of oil.

It has also been observed that sesame oil is degraded more slowly than viscoleo. Furthermore, experiments in which radiolabeled oils were injected into dogs showed that half the radioactivity disappeared from the injection site 2 days after the injection of ^{14}C-viscoleo, or 5 weeks after the injection of ^{14}C-sesame oil (Svendsen et al. 1979). The same workers also showed that chronic intramuscular injection subsequent disposition of oil in the lungs as microemboli. The authors expressed the view, based on their animal work, that should pulmonary oil microembolidation occur in patients receiving large volumes of oil, the pathological sequelae would probably be unimportant. Obviously more data are required on the long term toxicology of the injectable oils in humans. Moreover, Aaes-Jorgensen and coworkers (1977) have demonstrated high levels of clopenthixol decanoate in lung tissue from dogs given 30 or 100 mg/kg/week of clopenthixol decanoate in viscoleo. At present there are no human data on the possible migration of clopenthixol decanoate or any other depot pro-drug to lung tissue.

Pharmacokinetics of LINS

The fact that the drug is released very slowly from the oily depot has important effects on the pharmacokinetics of LINS. When a drug is administered orally, plasma concentrations rise to a maximum during what is called the "absorption phase" and then decline polyexponentially (in the case of most neuroleptics) in what have been termed the "distribution" and "elimination" phases. In this case, the elimination rate constant and half-life values are often calculated from the "terminal" portion of the log plasma concentration versus time curve. With the development of ultrasensitive analytical methods, however, it has become feasible to monitor plasma levels for several days after the administration of a single oral dose of neuroleptic. In one study, for example, plasma haloperidol levels could be measured for 11 days after the administration of a single oral dose of 5 mg haloperidol to a drug-free healthy volunteer (Hubbard et al. 1987). In this case, the "terminal half-life" was calculated as 21 days, which possibly represented a half-life for redistribution as the drug was slowly released from fat deposits and tissue binding sites. Where LINS are concerned, however, the very slow release of drug means that the absorption of drug from the depot into the blood stream takes place continually throughout the interval between doses. Thus, the pharmacokinetics of LINS are rate limited by the rate of absorption (release from the depot) rather than the rate of metabolism (Jorgensen 1980; Ereshefsky et al. 1984). In this situation the decline in plasma concentrations from the peak level reflects the rate of absorption rather than the elimination rate constant. Since the rate of absorption (release) is slower than the rate of elimination, the pharmacokinetics assume what has been termed a "flip flop" model (Gibaldi and Perrier 1982). Further discussion on the "flip flop" kinetics of LINS is available elsewhere (Ereshefsky et al. 1984; Jann et al. 1985). Suffice it to say that the polyexponential plasma level decline curve obtained after the administration of LINS is very difficult to interpret unambiguously, particularly in view of the fact that the curve is almost invariably contaminated by interference from drug leaching out of old injection sites and fatty deposits in the body. Under these circumstances it is not surprising that the drug can be detected in the plasma of patients for months after cessation of therapy with LINS (Gitlin et al. 1988). Therefore, a half-life value calculated from the "terminal" portion of the log plasma level time curve of LINS is not an elimination half-life. This situation has resulted in a great deal of confusion

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Time course of plasma levels

Fluphenazine enanthate and decanoate

There are clinically important differences in the kinetics of fluphenazine following the administration of the decanoate or enanthate esters. A sharp peak in fluphenazine levels occurs within 24 h of the administration of the decanoate but not the enanthate. This phenomenon was first observed by Curry and co-workers (1979 who administered radiolabelled materials, and confirmed by Wiles and Gelder (1979) and Midha et al. (1988) using radioimmunoassay techniques, and by Chang et al. (1985) by means of a GLC method. The reason for the early peak is unclear, although it has been suggested (Jann et al. 1985) that the decanoate may bind to muscle tissue differently from the enanthate and as a result may be more exposed to plasma and muscle esterases when first injected. More significantly, the use of the decanoate permits a longer interinjection interval because fluphenazine is more slowly released from the depot after injection of the decanoate compared with the rate of release after administration of the enanthate. For example, Curry and co-workers (1979) calculated from the decline in plasma radioactivity after the administration of 25 mg doses of radiolabeled drug, half-life values (for release from the depot) of 3.6 and 3.7 days after administration of the enanthate, and of 6.8 and 9.6 days after injection of the decanoate. Similarly, Dreyfuss et al. (1976a) found that the rate of release from the depot after administration of the decanoate to dogs was less than one half that after injection of the enanthate. As a consequence, the slower release and longer inter-injection interval makes the decanoate more convenient than the enanthate for use in patients.

After the initiation of therapy with fluphenazine decanoate, weeks or months are required for the establishment of steady state. Precise data on the time required to reach steady state are difficult to establish because patients are usually under medication with neuroleptics before commencement of studies on the depot preparation. Moreover, the lipophilic nature of fluphenazine and the prolonged period over which the drug is released from the depot is reflected in a tendency for patients treated with fluphenazine decanoate to have substantial plasma levels of fluphenazine for months after discontinuation of therapy (Wistedt et al. 1982; Gitlin et al. 1988). This has significance when patients who have been under medication with depot neuroleptic are entered in pharmacokinetic studies since withdrawal of the drug, even for a period of 3 months, may not be an adequate "washout" period. Thus, in one study, patients receiving biweekly injections of 5 mg fluphenazine decanoate were found to have reached steady state after the first injection because of fluphenazine resulting from prior therapy with fluphenazine decanoate administered before the period of study. On the other hand, patients receiving biweekly injections of 25 mg fluphenazine decanoate appeared to require 3–6 months (6–12 injections) to reach steady state (Marder et al. 1986). Similarly, in a group of patients treated with weekly injections of 50 mg fluphenazine decanoate, 10 weeks (ten injections) were required to reach steady state (Ereshefsky et al. 1984) although from theoretical considerations, these authors predicted a time to steady state pharmacokinetics of depot neuroleptics which require further investigation and more satisfactory answers than are available at present.

Haloperidol decanoate

Like fluphenazine enanthate, haloperidol decanoate does not give rise to an "early peak" in plasma levels which is characteristic of fluphenazine decanoate. In fact, peak levels of haloperidol occurred some 3–5 days after administration of the decanoate (Gelders 1986). Thereafter plasma levels of haloperidol declined very slowly, with a half-life of 3 weeks. Thus, the rate of release of haloperidol from the depot is somewhat slower than that of fluphenazine after administration of the respective decanoates. Like fluphenazine decanoate (Altamura et al. 1979), haloperidol decanoate appeared to be hydrolysed very slowly by plasma or tissue esterases in vitro (Nambu et al. 1987). It has also been reported that lymphatic uptake may play an important role in the slow release of haloperidol after administration of the decanoate (Gelders 1986).

Data on the clinical pharmacokinetics of haloperidol decanoate have been summarized in convenient table form in a recent review (Beresford and Ward 1987). Most studies appear to suggest that steady state levels of haloperidol are reached about 3 months after initiation of injections of haloperidol decanoate every 4 weeks. However, our previously mentioned reservations about data on fluphenazine decanoate also apply here. For example, De Cuyper and co-workers (1986) suggested that "relatively stable plasma levels of haloperidol were achieved with the first injection", although their data show that the mean trough plasma levels were still rising during the 2nd, 3rd and 4th months, after which te experiment was terminated. An interesting finding was that there was more rigidity and tremor during the first 2 months of treatment, but from the 3rd month, extrapyramidal symptoms were less pronounced than during the period on oral neuroleptics (De Cuyper et al. 1986).

Flupenthixol

Pharmacokinetic studies on flupenthixol decanoate have been reviewed by Jorgensen (1978). As is the case with haloperidol decanoate, there does not appear to be an early plasma level peak with flupenthixol decanoate. Jorgensen (1980) found that levels of *cis* (Z)-flupentixol rose slowly during the first 3–5 days after patients received an injection of *cis* (Z)-flupentixol decanoate. The descending portion of the plasma level time curve gave a half-life value of 3–8 days, which as indicated earlier, represents a half-life for release of drug from the depot rather than elimination. Thus, flupenthixol appears to be released from the depot more quickly than haloperidol, which may be partly due to the formulation of flupenthixol in viscoleo rather than sesame oil, partly due to the more rapid hydrolysis of flupenthixol decanoate which has been noted in in vitro preparations (Jorgensen 1978).

Relationship of plasma level and clinical response

Unfortunately, there have been very few studies of the relationship of clinical response and plasma levels for patients

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double-blind comparison that involved either being continued on their current regimen of FD or having a placebo substituted for their FD. In the 14 patients who continued on FD (mean dose, 21.4 mg), they found that patients who relapsed on FD had lower plasma levels (0.92 ng/ml) than those who did not relapse (1.36 ng/ml). Marder and coworkers (1986) studied plasma levels in patients randomly assigned to a double-blind comparison of 25 or 5 mg FD administered every 2 weeks. Since it required nearly 6 months for the higher dose patients to reach a stable steady state, the authors compared levels at this stage of treatment for patients who either relapsed or remained stable. Although the mean fluphenazine level was lower for patients who relapsed (0.57 ng/ml for relapsers versus 1.01 ng/ml for nonrelapsers) this difference was not statistically significant. Ereshefsky and coworkers (1984), on the other hand, found a lower therapeutic threshold (0.2–0.4 ng/ml) for a patient group treated with either oral fluphenazine or fluphenazine decanoate.

Effects of neuroleptic metabolites

Some of the antipsychotic effect of neuroleptics may not be related to the parent drug, but rather to psychoactive metabolites of the parent drug. For example, important major metabolic pathways of phenothiazine neuroleptics include sulfoxidation, N-oxidation, oxidative N-dealkylation, ring hydroxylation and glucuronidation. However, the parenteral administration of LINS avoids first pass metabolism, and may, therefore, minimize the impact of metabolites.

Perhaps the best studied metabolic pathway for the phenothiazines involves the oxygenation of the ring sulfur atom to form sulfoxide derivatives. Early reports (Dahl 1976; Dahl and Strandjord 1977) suggested that sulfoxide metabolites could be found in plasma after the oral administration of phenothiazines, but not after the parenteral administration and it has been suggested that metabolism occurs during passage through the gut wall (Curry et al. 1971). However, Hartmann and co-workers (1983) have reported minimal metabolism and chlorpromazine in samples of small intestine taken from a disease-free accident victim. Evidence that sulfoxidation actually takes place in patients treated with fluphenazine decanoate is provided in a recent report by Midha and his collaborators. The presence of fluphenazine sulfoxide in the plasma and urine of patients on FD was proved by powerful modern GLC-MS procedures (Edom et al. 1986). Using a RIA method which had been confirmed by GLC-MS, fluphenazine sulfoxide was found in 97% of samples taken from 30 schizophrenic patients who had been maintained on chronic FD without any dosing with oral fluphenazine (Midha et al. 1987). Interestingly, the levels of fluphenazine sulfoxide were nearly as high as those of the parent drug. Since there was a considerable amount of variation in sulfoxide levels among patients, it is conceivable that differences among patients in metabolism may be clinically important.

The impact of changing a patient from oral to depot fluphenazine on plasma levels was demonstrated in a recent (unpublished) study from our laboratory. We were interested in differences in drug metabolism between the oral and depot forms and whether there was a relationship be-

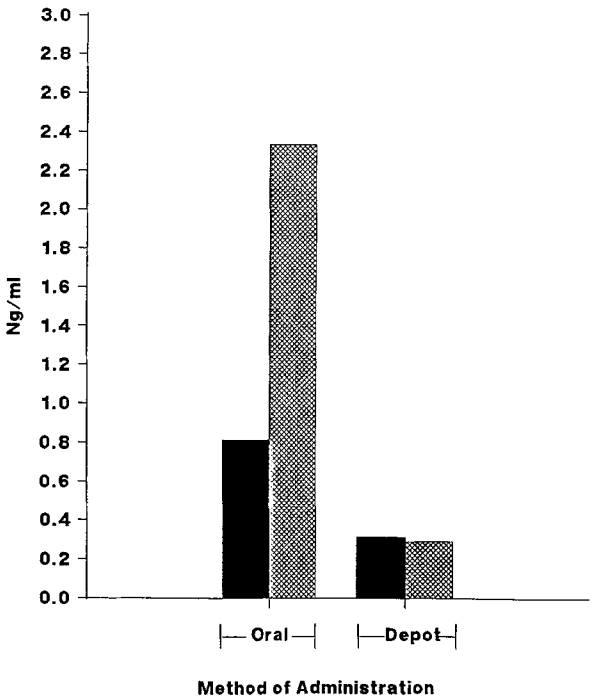

Fig. 1. Mean fluphenazine (F) and fluphenazine sulfoxide (FS) levels in eight patients who were initially treated with oral and subsequently changed to fluphenazine decanoate. The difference in ratio between FS to F was: $t=7.16$; $P=0.0002$. ■ Fluphenazine; ▩ fluphenazine sulfoxide

Eight newly admitted psychotic patients were randomly assigned to receive 5, 10, or 20 mg oral fluphenazine for at least 4 weeks. After 1 week (when orally treated patients should have reached steady state) blood was drawn in the morning 12 h following the previous oral dose. Following stabilization, patients had the oral drug discontinued and fluphenazine decanoate was administered in doses between 5 and 25 mg every 2 weeks. Blood was drawn again after patients had been on the same dose of the depot drug for 3 months. Sampling this time was done 2 weeks after the prior injection. Plasma levels of fluphenazine and fluphenazine sulfoxide were measured using previously described radioimmunoassays (Midha et al. 1980, 1988). As noted in Fig. 1, the levels of both substances were lower for the intramuscular route. This is consistent with the intention of the clinician to use the lowest effective dose for maintenance therapy. Moreover, the difference in the ratios of the parent drug to its sulfoxide metabolite is also interesting. In the orally treated patients, the concentration of the sulfoxide metabolite was approximately 3 times the concentration of the parent drug, whereas the patients on depot drugs had levels of parent drug and metabolite that were similar ($P=0.0002$). This supports the view that sulfoxidation of the parent compound is likely to be a much more important factor for patients treated with an oral as opposed to a depot phenothiazine.

The clinical importance of the sulfoxide metabolite of fluphenazine is currently unclear, although most of the evidence indicates that sulfoxidation of a phenothiazine neuroleptic renders the drug relatively inactive (Dailey et al. 1972; Bunney and Aghajanian 1974; Dahl 1982). An excep-

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mine blocking activity. Bylund (1981), on the other hand, studied the in vitro binding of fluphenazine sulfoxide to dopamine receptor sites and found that the drug had substantially less affinity than the parent drug. It appears likely, therefore, that the lower amount of sulfoxidation in patients treated with a depot drug results in the drug being more biologically active at the appropriate receptor sites.

Relationship of plasma level and dose

One of the possible advantages of LINS over oral forms is that there may be a closer relationship between the drug dose administered and the resultant plasma level. The clinician would, therefore, be less likely to overtreat or undertreat a patient with the parenteral form. This is a theoretical advantage of LINS which is based on the belief that depot drugs are not associated with an important source of between-subject variance that exists with oral drugs; that is, the amount of first pass metabolism.

For haloperidol decanoate, there appears to be a relatively high correlation between dose and plasma level (De Buck et al. 1981; Reyntjens et al. 1982; De Cuyper et al. 1986). However, the relationship of plasma level to dose differs among the LINS. McCreadie and associates (1986) have reported less variation in neuroleptic plasma levels with haloperidol as compared to fluphenazine decanoate. This difference parallels studies of the counterparts of the two drugs with oral haloperidol also demonstrating less variation in plasma levels when compared with oral fluphenazine. Lower variation with haloperidol may result from the simpler metabolism of this butyrophenone type of antipsychotic.

As mentioned previously, the metabolism of phenothiazines such as fluphenazine appears to be more complex and involve larger numbers of metabolites. The presence of these metabolites may explain why studies which investigated the relationship between plasma level and dose with fluphenazine have generally not found a strong relationship. An exception is a study by Cohen and associates (1985) which found a correlation of 0.75 ($P<0.0001$) between blood level and dose for patients treated with decanoate and enanthate esters. This later study differed from others in that a radioreceptor (RRA) method was used. Since the RRA measures the activity of both the parent compound (that is, fluphenazine) as well as its active metabolites, it may be that Cohen's strong relationship was present because a major source of variation between patients, namely the differences in drug metabolizing capacity, is decreased.

Clinical implications of pharmacokinetics

Early peak plasma levels

Fluphenazine decanoate plasma levels often peak during the first day or two following an injection. We are not aware of any clinical data that suggests that this peak has a clinical impact. However, Ayd (1973) has stated his clinical impression that patients treated with fluphenazine enanthate or fluphenazine decanoate often demonstrate severe neurological side effects during the first 12–24 h after an injection. We have noticed occasional patients who report

Length of time to steady state

As mentioned previously, one of the reported characteristics of LINS is a very lengthy period of time until they reach a stable steady state. For example, Marder and his coworkers (1986) found that patients treated with 25 mg of fluphenazine decanoate required 3–6 months before reaching a steady state. Others (Gelders 1986; McCreadie et al. 1986) have reported similar results for haloperidol decanoate, although Deberdt and coworkers (1980) reported that haloperidol reached a steady state after only two monthly injections.

The length of time that it takes LINS to reach a steady state can be a significant problem. If the clinician is cautious with dose and starts the patient off on a relatively low dose, there is likely to be a significant period of time – perhaps 1–3 months – during which the patient may be significantly undertreated. This would result in the patient being more vulnerable to relapse. If too high a dose is selected, the patient may be exposed to a dose which is higher than necessary and perhaps even toxic. Three possible solutions to this dilemma are: (1) supplement the patient with oral medication during the vulnerable months when the depot drug is reaching a stable steady state, (2) start the patient on a high or loading dose of LIN during the first injections and decrease the dose during subsequent injections, and (3) use a shorter interinjection interval for the first injections.

Use of oral supplementation during the change to LIN

The usual clinical practice – particularly following an acute episode of schizophrenia – is to stabilize patients on an oral medication and then switch to an LIN. This is because LINs are rather poor for the initial stages of treatment since it is much more difficult to titrate the dose against clinical response. The change from oral to depot medications may correspond to a time when the clinical goals are changing. That is, patients receiving oral therapy may be receiving treatment for an acute psychosis. Once stabilized, the clinician may decide to change to treatment with a LIN at about the same time that the patient is demonstrating substantial improvement in schizophrenic symptoms. Common clinical practice includes lowering the dose of neuroleptic after the patient has recovered from the acute episode. This practice is supported by Baldessarini et al. (1988), who reviewed studies of the dosage requirements for acute and maintenance therapy and found that the effective dose for therapeutic effects in 50% of patients (or the ED_{50}) for the treatment of acute schizophrenic illness was about 340 mg chlorpromazine daily, and 50–150 mg for maintenance treatment. In other words, any plan for deciding on the dosage for maintenance therapy should be based upon an evaluation of the patient's clinical state at the time of the changeover. For example, Baldessarini and coworkers have computed an ED_{50} of 5 mg every 2 weeks for fluphenazine decanoate. However, the studies on which this figure is based (Rifkin et al. 1977; Hogarty et al. 1979; Kane et al. 1983; Marder et al. 1984) usually involved patients who had been well stabilized and may not be relevant for individuals who have recently recovered from an acute episode.

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