Long-Acting Antipsychotics

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Long-acting (depot) anti-psychotic injection (LAI) is an essential component of the treatment of schizophrenia. In this editorial, the journal tries to give a short account of the current ideas and practical aspects of LAI, with respect to the Iranian experience. Two categories of the Long-acting injections are discussed; mainly regarding their dosage, intervals of their injections and availabilities.

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"Doctor, your patient doesn't take his medication you have prescribed for him. Is it possible to give him injections?"

Most of us have been faced with such a question in our every day practice which is put to us by the patient's relatives. It is well established that antipsychotic medications are an essential component of the treatment of schizophrenia as well as other psychiatric disorders with prominent psychotic symptoms (1,2), and consistent administration of these drugs is often what enables other treatment modalities accepted (3).

The question is why these patients who need the medication are non-adherent to their antipsychotics. The reasons they do not take their medications are: a. they think they are not sick, therefore there is no need to take the medication, b. they are well now and there is no need to continue to take the medication, and c. the side effects, which are really troublesome, prevent them of continuation of treatment. It is also well established that about 40-60 percent of patients with schizophrenia are known to be non-adherent to oral antipsychotic medication (4). Even within relatively compliant patients, a large range of health beliefs and widely varying degrees of insight exist, which, in turn, are important contributors to treatment adherence (5). Therefore, there is definitely a place for Antipsychotic Long-acting Injections (LAIs) in the long term management of schizophrenia and other psychotic disorders. However in many countries throughout the world fewer than 20% of patients with schizophrenia receive these medications (3).

When all of the data from individual trials and meta-analyses are taken together, substantial evidence indicates that LAIs have advantages for psychotic patients during maintenance treatment (3). In addition to partial solution of poor compliance, LAIs are also associated with less variability between patients in steady-state blood serum levels for a given dose than are oral formulations, because depot antipsychotics bypass variations in drug absorption and first-pass hepatic and gastrointestinal metabolism. Therefore, these drugs are more effective than oral antipsychotics for preventing relapse in stabilized patients (6). Also, it has been demonstrated that risk of deliberate or accidental overdose with antipsychotic medication is avoided by depot prescription (7). In most textbooks of psychiatry, rather limited space has been given to this important aspect of the treatment. In particular, practical issues are untouched (6,8-10). As it has been demonstrated that prescribing habits vary

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greatly within a region and between regions of one country (11), we should like to elaborate more on this issue, particularly with respect to the Iranian experience.

The 1st LAI was fluphenazine enanthate in 1966 and the second, some 18 months later, was fluphenazine decanoate (2).

There are two groups of LAIs: First-generation LAIs and Second-generation LAIs. There are six first-generation LAIs in the market, namely, flupenthixol decanoate, fluphenazine decanoate, haloperidol decanoate, perphenazine decanoate, pipotiazine palmitate and zuclopenthixol decanoate. There are two second generation LAIs available in the market, namely olanzapine pamoate and risperidone microspheres (12). Previous experience, personal patient preference, patient's history of response (both therapeutic and adverse effects) and pharmacokinetic properties should be considered in choosing one of these drugs for treatment of psychotic disorders (3).

Some clinicians suggest stabilizing a patient on the oral preparation of the specific drug before initiating the long acting injectable form. Some others suggest giving at least one oral dose of the drug to assess the possibility of any untoward adverse effect, such as severe extrapyramidal and allergic side effects. Moreover, absorption of LAIs may be faster at the onset of prescription, and initiating this form of the drug with full dose may lead to severe side effects that may encourage noncompliance with depot medication. To deal with this problem, some authors suggest initiating the LAIs with very small doses (8).

It is worth mentioning that in Iran there are only three first generation LAIs. These are fluphenazine decanoate, flupenthixol decanoate and haloperidol decanoate (13). Fluphenazine decanoate has been used more in Iran and most psychiatrists have experiences in using them. Oral preparation of this drug (1 and 2.5 mg tablets) is also available in Iran. A test dose of 12.5 mg IM is recommended and after a week or two the dose should be adjusted according to the need of the patient and side effects (12). The initial dose may be as low as 3.125 mg to avoid frightening episodes of acute dystonic reaction (8). The usual dose per 2 weeks is 25-50 mg IM. Licensed dosing interval varies in different countries (12). For example in UK is 2-5 weeks. In Iran there is no licensed dosing interval, but most psychiatrists give fluphenazine decanoate in 2 to 4 weeks intervals. The available fluphenazine decanoate injection is 25 mg ampoules. For haloperidol decanoate - the third available LAI in Iran - there is no fixed test dose in most literature, but it is usual practice of most psychiatrists to give a test dose of 25 mg IM; after a week or two the dose has to be adjusted according to the need of the patient and side effects (12). Conservative initial dose of haloperidol decanoate may be as low as 6.25 mg every few days to avoid adverse effects related to rapid initial absorption of the drug (8). The usual dose per 2 weeks is 100 mg IM. The licensed dosing intervals in UK is 2-4 weeks (12). The available haloperidol decanoate injection is 50 mg ampoules. It is worth mentioning that in Iran the usual dose of haloperidol decanoate is 50 mg IM injection 2-4 weeks intervals. Oral preparation of this drug (0,5 and 5 mg tablets) is also available in Iran. The third available LAI is flupenthixol decanoate. Oral preparation of this drug is not available in Iran. It is given initially as a test dose of 20 mg. After a week, a further dose of 20-40 mg is given. Typical clinical dose per 2 weeks is 60 mg and licensed dosing intervals in UK is 2-4 weeks (12). In Iran, the usual dose is 20-40 mg IM, 2-4 weeks intervals. The available flupenthixol decanoate in Iran is 20 mg ampoules. It seems that flupenthixol decanoate has less sedative side effects compared to other available LAIs in Iran. Usually after at least five times the half-life of a LAI, most of these drugs approach steady-state plasma concentration (8). However, it should be mentioned that fluphenazine and haloperidol decanoates can take up to 6 months to reach steady state plasma levels, indicating that the oral therapy should perhaps be continued during the first month or so of depot antipsychotic injection (8).

Of the two second generation LAIs, none is widely available in Iran. Olanzapine pamoate is

not available at all. In fact there are limited clinical experiences with olanzapine pamoate due to its recent introduction to the market in the world. Test dose is not recommended for olanzapine, and typical clinical dose per two weeks is 300 mg (12). Risperidone LAI is available by limited pharmacies in Iran, called "single prescription pharmacies". Treatment with risperidone long-acting injectable microsphere has been resulted in clinical improvement in patients switched from first generation LAI to this drug (10). Risperidone microsphere test dose is not appropriate. Typical clinical dose per 2 weeks is 37.5 mg (12). The available risperidone microsphere is 20 mg ampoules. Another problem with risperidone LAI is the price. It is very expensive. If a patient is on 20 mg injection every 2 weeks, it would cost him/her 2500000 to 3000000 Rials per month which is close to the monthly minimum wage of the country. Depot antipsychotic may be associated with more adverse effects, including tardive dykinesia, neuroleptic malignant syndrome, and particularly extrapyramidal symptoms. Although this concern is controversial, clinicians should probably refrain from using depot forms unless the patient is unable to comply with oral medications (3,8,14-16). Some Iranian psychiatrists prescribe long acting injection for their patients who are also on oral antipsychotics routinely. Such a practice is not advised.

It is worth mentioning that some psychiatrists give anticholinergic injections when administering LAIs at the same time. In a rather old textbook of psychiatry called Companion to Psychiatric Studies edited by A. Forrest one reads (13), "oral anti-parkinsonian drugs (i.e., orphenedrine) are given for four to five days after each injection." There is no recent satisfactory evidence for such a practice. I think that if extrapyramidal side effects appear oral anticholinergic must be given to the patient and there is no need for simultaneous anticholinergic injection when administering LAI. Due to euphoric properties of anticholinergic medications, many patients abuse oral and particularly injectable anticholinergics. Many psychiatrists encounter patients abusing more than 10 injectable anticholinergics per day.

Despite the fact that the use of depot injection has decreased in recent years, perhaps owing to the introduction of atypical antipsychotics, any patient for whom long-term treatment is indicated should be considered a candidate for LAI (4). There are few second generation LAIs available; however we should wait for the introduction of new LAIs with acceptable effectiveness and less side effects in the future.

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