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Drawbacks of Long-Acting Intramuscular Antipsychotic Injections

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Abstract

Second-generation antipsychotics have relatively recently become available in long-acting intramuscular formulations (LAIs) and have been receiving a substantial amount of pharmaceutical industry promotion on the grounds that they improve treatment adherence in patients with psychotic illness. LAIs do have some drawbacks, however, which is the topic area covered by this review. A Global Scholar search of the nursing and medical literature reveals several factors that can negatively impinge on the clinical efficacy of LAIs: 1. The extent of training of injection personnel 2. The quality of surveillance of patient symptoms and side effects 3. The skilled use of the full range of injection techniques 4. The extent of drug accumulation over time 5. The potential loss of drug dose flexibility 6. The impact of exercise and temperature on drug distribution 7. The burden of the medication routine and the social burdens of LAIs 8. The safety of LAIs during pregnancy 9. The perceived coerciveness of LAIs 10. Issues of overdose and polypharmacy 11. Issues of cost 12. The important issue of responsibility for self-management of illness. Although the evidence is clinical and anecdotal, LAIs appear to work well for many patients, but their drawbacks are not negligible. Clinicians need to weigh individual risks and benefits when making treatment decisions.

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Introduction

Long-acting intramuscular formulations of antipsychotics medications (LAIs) have been in clinical use since the early 1960s for the treatment of schizophrenia and related conditions. Second-generation antipsychotic LAIs have been made available more recently. An LAI means that the active drug is injected into a large muscle from where it gradually disperses, usually over several weeks, into the bloodstream and, hence, into the brain where it attaches to target neuroreceptors that control the transmission of key neurochemicals. By partially blocking transmission, the drug prevents the emergence of psychotic symptoms. The assurance of a long duration of blockade offers many advantages for patients who suffer from chronic forms of psychosis. The injection obviates the task of taking oral medications on a daily basis, a problematic task for many individuals who are diagnosed with schizophrenia and related conditions. It is easy to forget to take the daily pills, to run out of pills before a new prescription can be filled, or to abandon pills altogether when side effects emerge, or when one decides that medication is not needed. Because stopping antipsychotic medication leads to a very high rate of psychotic relapse, relatively strict adherence to a prescribed regimen is usually critical to well-being. LAIs, which are consistently reported to markedly improve treatment adherence[1], are important in this context. Should the patient miss an injection, the treating personnel is immediately aware of the lapse and able to reach out to the patient to negotiate a quick resumption of medication. Another distinct advantage of LAIs is that they bypass gastric absorption, an important benefit for elderly patients with impaired absorption. The superior efficacy of LAIs over oral antipsychotic medications with respect to symptom reduction in psychosis has also been reported, but this latter claim has been difficult to prove[2]. On balance, the currently available evidence indicates that LAIs are at least as effective as oral antipsychotics and most likely more effective in specific groups of patients, such as those who tend to relapse frequently[2]. Nevertheless, drawbacks to the use of LAIs have also been reported[3]. Since patents on the most popular second-generation antipsychotics have expired and these oral medications are now available in generic form, pharmaceutical companies have begun to actively promote the benefits of the still patented long-acting injectable formulations. Clinicians may not be sufficiently informed about potential drawbacks, which is the reason for this review paper. Knowing both pros and cons will help clinicians individualize treatment decisions.

Method

The first step in undertaking this review was to search the nursing and medical literature in Google Scholar with the following search terms: Long-acting antipsychotic, depot antipsychotic, intramuscular antipsychotic. This initial probe was followed by a search of published guidelines relevant to the administration of long-acting intramuscular antipsychotics. By the end of both search strategies, several findings relevant to the effectiveness and safety of LAIS had emerged from the published literature. They were: 1. The person who administers the injection requires training and

experience 2. Accurate symptom and side effect surveillance is critical to safety 3. The injection technique needs to be adjusted to specific individual needs and also to the specific nature of the injected compound 4. Drug accumulation over time can be a problem, but can also be a benefit 5. Dosing flexibility is lost when a person receives an LAI and no oral medication 6. Drug dispersal from the muscle site of the LAI is affected by exercise and by heat 7. LAIs pose specific treatment burdens on the patient 8. LAIs are not considered safe during pregnancy 9. LAIs may be perceived as coercive 10. LAIS lower the risk of overdose but increase the risk of polypharmacy 11. The cost of LAIs may be an issue for some patients 12. Personal agency and the possibility of self-management may be lost for patients on LAIs. This review summarizes what is known about these twelve topics in order to aid clinical decisions.

Findings

The importance of continuity, training, and experience in injection giving Long-acting intramuscular formulations have been reported to be more effective than orally administered drugs for patients with schizophrenia in both naturalistic studies and in clinical trials[4]. Nevertheless, these two conditions of practice are very different. In contrast to what happens in a clinical trial, in everyday clinical practice there may not be a well -trained research nurse available to administer the injection. The nurse who does give the injection will probably not be following a standardized research protocol. Patients receiving the injection will not be receiving any compensation and may not be attending the injection clinic voluntarily. In everyday practice, the nurse on duty will generally have several competing obligations that do not allow for quality time spent with patients. Her availability may be limited. She (or he) may not be familiar with the whole range of alternate injection techniques and needle lengths that guidelines recommend for specific patients. The nurse will probably not be using a validated instrument to monitor potential psychotic symptoms and drug side effects. Should unexplained symptoms emerge, or unexpected adverse effects, or behavioral issues, the nurse may not have immediate access to expert consultation, which she would have if this were a clinical trial.

In real life, a variety of people in a wide range of settings may be the ones to administer an LAI. It may be a community nurse in the patient's home or a psychiatric nurse in a hospital clinic, or an office nurse in a family doctor's practice. Sometimes, the primary physician or the psychiatrist gives the injection. The injection provider may be a different person from week to week; continuity in that role is difficult to maintain. The person may, or may not, be well-trained. Experience varies widely among real life injection givers, as does the amount of time they can spend with the patient, the depth of their knowledge about the patient's background and illness, their ability to accurately detect changes in the patient's mental state, and their ability to recognize drug side effects.

Case Example from My Practice

In the 1970s, one of my patients was receiving

long-acting fluphenazine decanoate every three weeks to treat long-standing psychotic illness. When the patient started a 9 to 5 rehabilitation program, I was unable to see her after hours so an evening-shift nurse offered to see the patient, administer the injection, and act as a liaison between the hospital and the rehabilitation program. The nurse and I met regularly to discuss the patient's progress. After a few months, I was told that the patient was not doing well in the program. The rehabilitation staff complained that she was "acting hysterical, grimacing at male patients in a flirtatious way, inappropriately winking at them." The nurse talked to the patient about this behavior, but it got worse rather than better. Eventually, the rehabilitation program asked the patient to leave and I was able to see her again. The grimacing and winking and inappropriate behavior turned out to be drug-induced tardive dyskinesia, unrecognized by the nurse and by the rehabilitation personnel. Signs of tardive dyskinesia in the 1970s were not infrequently dismissed as "hysterical"[5].

Symptom and side effects monitoring

In real life, patients with long standing psychotic symptoms are difficult to engage in counseling and are often seen only summarily by their psychiatrists – infrequently and for very brief appointments. When patients are taking oral medication, pharmacists require the periodic renewal of the prescription, which guarantees periodic face-to-face visits with the doctor. When patients receive depot injections, hospital regulations sometimes allow written prescription renewals without face-to-face meetings. Months may go by before a patient's symptoms and side effects are medically checked. This, of course, can be corrected by training the nurse who gives the injections to monitor medical symptoms and adverse effects, and by changing hospital regulations to require all psychiatrists to see their patients regularly whether on medication or not.

Case Example from My Practice

A memory that stands out for me is that of a patient who had been coming for monthly depot injections for two years without telling anyone at the clinic of a lesion on her breast and without anyone noticing her severe weight loss until her breast cancer had become inoperable.

The importance of injection technique

The perfection of proper technique for administering long acting injections of antipsychotics requires training and practice[6]. Techniques vary according to the specifics of the patient and the nature of the injection; different gauge needles are recommended for different injection sites and for different drug formulations. Decisions about sites and needle lengths are usually based on patient factors – the very thin or very obese patient, the patient who refuses gluteal injections, the patient who develops nodules or abscesses or needle injury. Unless needles are sufficiently long, the drug can land up in the subcutaneous fat of obese patients rather than in the muscle[7-11]. Local reactions can depend on patient factors, but also on the nature of the drug and the frequency of the injections. Depot fluspirilene for

instance, which is given once a week has been several time reported to provoke local reactions[12,13].

Depending on the skill and experience of the injector, injections can be painful, can sometimes by accident enter a blood vessel[14], can sometimes cause local infections[15], untoward local tissue responses (16,17), sciatic nerve injury[18,19], or even glass contamination[20]. Sciatic nerve injury is most likely when the dorsogluteal site is the chosen injection site. Because sciatic injury can result in leg pain, muscle weakness and wasting, numbness, and impairment of gait, sleep, and can interfere with normal functioning, experienced nurses often choose the ventrogluteal site that avoids the sciatic nerve, but the use of this site requires extra training[21-25]. While current research recommends the ventrogluteal site, when nursing choices were probed at two time points (2006 and 2012), the dorsogluteal site was still being more commonly used, suggesting that practice lags behind evidence. In addition, there are many proponents of the deltoid site[26-28], which is considered more respectful of patient dignity, only requiring exposure of the upper arm. Physical injuries sustained by different injection techniques can be compared by ultrasound examination[29], but this is not routinely done.

Drug accumulation

Long-acting injections are usually given every two, three, or four weeks on the assumption that the muscle store is depleted at the end of that period. Antipsychotics being lipophilic drugs, however, a portion of the drug is stored in the body's lipid repositories and can accumulate there over time[30], often more so in women than in men because of women's relatively more extensive lipid depots. This can be an advantage in that it lengthens the time between stopping an injection and the return of psychotic symptoms, the drug continuing to seep into the bloodstream from fat stores long after muscle stores are depleted. Accumulation can also cause unexpected problems, however, as the following case illustrates:

Case Example from my Practice

A 40 year old woman who had been on depot antipsychotic injections for ten years joined Weight Watchers and lost 40 pounds in three months. Accumulated drug from her dwindling fat stores entered her blood stream and, in turn, her brain, which led to the development of very distressing extrapyramidal symptoms, side effects of her medications. She didn't know what they were because she had never before experienced side effects.

Such experiences and currently available brain imaging data raise the possibility that, in some patients, the dosing interval of LAI antipsychotics may – and should - be extended beyond the currently recommended time period[31].

Dose flexibility

Depending on chance events and exposure to stresses, the dose of antipsychotics often needs to be adjusted up or down. Depot treatment leaves little room for such adjustments[32] unless concomitant oral drugs are added to the regimen. By the same token, once the drug is in the muscle and side effects develop, they can

remain unalleviated for a very long time. In the early years of antipsychotic drugs, there were many reports of unusually severe and prolonged side effects from LAIs[33], but this is less so now in the era of second-generation antipsychotics.

Case Example from My Practice

In 1963 when I was a resident in psychiatry, I worked on a unit that evaluated new drugs and we tested the first long acting injection, fluphenazine enanthate, expected to be effective for two weeks. The first person we gave it to (I no longer remember the dose we gave but it was probably the one recommended at the time – 25 mg) developed unmanageable akathisia. She paced up and down the ward non-stop day and night and no sedative or anticholinergic or antihistaminic drugs were able to help. This continued for two months, far longer than the anticipated two weeks. The memory of that patient and her distress has made me very careful about prescribing long-acting antipsychotic medication.

The effect of exercise and heat Because injections are usually given into the gluteal muscle, exercising the leg will increase the flow of drug from muscle to bloodstream and will increase side effects. I have previously written about my experience with a patient to whom this happened[34]. Temperature (increased during exercise) may also cause more drug to enter the bloodstream. Patients need to be made aware of this possibility otherwise the sudden appearance of side effects can be frightening.

Burden

Mohammed et al.[35] have categorized the burden borne by patients when they take medications into the following categories: (A) burden imposed by medication routines, (B) specific burden of individual medications, (C) burden of specific adverse effects, (D) medication-related healthcare burden, and (E) medication-related social burden.

With respect to (A), medication routines, many people prefer coming for a monthly injection to the responsibility of remembering to take pills once or more times a day[36] and remembering to re-order them from the pharmacy once a month. Currently, 3-monthly depot injections are being promoted, which would make the medication routine even less onerous, although remembering to keep one's appointments might prove paradoxically more difficult[37,38]. The burden of remembering injection appointments can be transferred to the treating team by tasking them with the responsibility of telephone reminders to their clients. Medication routines may be onerous because of postponements due to sickness (of patient or nurse), or transportation difficulties, or official holidays falling on treatment days. The difficulties of out-of-town travel when on depot medication have been mentioned in previous reports[39]. Many patients find waiting in line at injection clinics hard to tolerate. Such waits are especially long for patients on olanzapine depot[40]. The olanzapine depot formulation carries the risk of a post-injection delirium sedation syndrome (PDSS), occurring in 0.07% of injections or 1.4% of patients. PDSS is caused by the accidental intravascular injection of the

drug, olanzapine depot being more soluble in blood than in muscle. Among the signs and symptoms of this syndrome are dizziness, confusion, slurred speech, and sedation. Symptoms usually start gradually, between 5 minutes and 5 hours after injection, and disappear between 24 and 72 hours post injection. The usual clinical requirement, therefore, is that the patient stay under nursing observation for at least 3 hours. On the positive side, wait time at clinics may be opportune for visiting with fellow patients, sharing a meal, and bonding together. It is often the part of the injection experience that patients most value. In fact, patients on injections are more likely than others to attend therapeutic programs after hospital discharge[41].

The social burden of injections (E above) refers to the need to explain to others why one has to be away from school or work or social engagements in order to receive periodic injections. Most patients are unwilling (and have reason to be) to share their need for psychiatric care with employers[42,43]. An easy solution would be the availability of evening depot clinics, but they are seldom available.

Pregnancy

Most psychosis treatment guidelines recommend *not* giving LAI to women planning pregnancy, pregnant, or breastfeeding[44]. Exceptions are made for women well established on depots who are stable and for whom discontinuation might usher in a period of relative instability. The recommendation is based on potential harm to the fetus or neonate from too large a bolus of drug. A patient in my practice did deliver prematurely immediately following the administration of a depot medication in her seventh month of pregnancy; the child was born with many congenital defects[45]. On the other hand, several successful outcomes of depot treatment during pregnancy have been reported[46-48].

Perception of coercion

Some patients, though far from all, perceive depot antipsychotics as being more coercive than oral medications[49-53]. The occasional patient may associate the needle with the memory of an involuntary injection in the past, administered during an acute disturbance. The assembly line quality of depot clinics may contribute to the perceived inhumanity of receiving injections. The fear of being controlled by the physician has been reported[54]. Being injected has been described as being put into a "chemical straitjacket"[55]. Injections have been stigmatized[56,57] because they have come to be considered as "last resort" treatments for the most severely ill, the most aggressive, or the most uncooperative patients. In addition, many patients consider it demeaning and dehumanizing to expose their buttocks to a nurse in order to obtain an injection[58]. Deltoid injections, whenever possible, would obviate that problem.

Overdose risk and polypharmacy

On the plus side, when a person is receiving depot injections, there is no risk of committing suicide by taking an overdose. This advantage is reduced, however, by the fact that people on injections are often prescribed concomitant oral medications as well. Polypharmacy is more common in those prescribed an LAI[59] than in those on an oral antipsychotic. The reason

why is not clear. It may be in order to increase flexibility in dosing or in order to counter side effects or because of the heightened illness severity of the population who currently receives LAIs.

Cost

Cost of the newer injectables is high and can be a major problem for patients when the injection is not covered by insurance or by the hospital pharmacy budget. This is, of course, true for all relatively new medications. For hospitals or clinics, there is also the cost of storage of injectables, some requiring refrigeration. To this needs to be added the cost of extra staffing of "depot clinics"[60,61].

Self-management

The most important quarrel with the practice of depot injections is that, while putting an emphasis on patient compliance, the LAI takes away a measure of autonomy and makes it difficult for the person to learn by experience[62]. Learning theory teaches that people learn not by being told what to do or having it done for them but by making their own discoveries through trial and error[63]. Patients with symptoms profit by learning what brings on their symptoms and what alleviates their symptoms. By occasionally forgetting to take their pills they learn that, though their side effects may improve, their symptoms get worse. Patients realize with time that there is a direct relationship between the severity of their symptoms and their daily dose of antipsychotic medication. This is important learning that allows the patient to take charge of his or her condition. On depot, patients are unable to take extra medication to help them over a period of increased stress. They are unable to establish control over their symptoms. Moreover, they cannot, when experiencing a distressing side effect, alleviate it by missing a dose or temporarily halving the dose[64].

Long-acting medications take months to achieve steady states after dose adjustments so that the patient remains passive vis à vis his or her treatment[65]. True patient-centered care requires knowledgeable patients who are able to discuss their experiences with their care providers and work with them to achieve recovery[66, 67]. Because individuals with psychotic disorders often report that their thoughts and sensations are influenced or controlled by external agents, it is especially important in this population to discourage passive dependence on others and to encourage and reinforce a sense of agency[68].

Discussion

This review, while citing some results from randomized clinical trials, has relied mainly on qualitative reports and clinical observation. This is an important limitation of the generalizability of the findings, a limitation that clinicians must bear in mind when making clinical decisions. Despite wide use, the findings of this review suggest that LAIs have drawbacks, which, in some instances, may be serious. A background concern is that the increasing enthusiasm for LAIs is based not on newly discovered cost effectiveness evidence for these formulations[69] but, instead, on the pharmaceutical industry's loss of patent protection of second generation oral antipsychotics. Long-acting formulations continue

under patent and this may account for some of the extra promotion they are receiving.

Conclusion

A thorough reading of the relevant literature confirms that long-acting antipsychotics have proven effective in schizophrenia and related psychotic disorders probably because of the stability of dose administration and the increase in treatment adherence[54]. On the downside, however, dosing flexibility is lost and the learning of self-management skills may be undermined by long-acting depots. Clinicians will need to consider individual risks and benefits when making treatment decisions designed to benefit individual patients.

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