



Original article

Problems with the Administration of Antipsychotic Drugs in Depot Formulations in the Treatment of Schizophrenia

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SUMMARY

The aim of this study was to investigate problems with the administration of antipsychotic long-acting injections (LAIs) in patients with schizophrenia. Besides many benefits, long-acting injections have been associated with a number of complications at the site of the injection.

The qualitative study included four medical workers and five patients who had been treated with fluphenazine, haloperidol, risperidone given in the form of a long-acting depot injection. The data were collected by direct observation, analysis of the history of the disease and used semi-structured interview.

Interviews completed by patients, psychiatrists and nurses were analyzed and condensed into nine key categories: Competence and training of the medical workers, Sites and technique, Registration of complications, Care of patients and privacy, Availability and evidence, Duration and frequency of treatment, Burden for the patients, The choice of formulation therapy, and Sense of stigma.

Monitoring of side-effects of LAIs was not extensive and doctors did not write adverse effects. The nurses who administered the injections were competent. Not enough attention is paid to the choice of the needle diameter and the patient was not given a choice to decide on the sites of the administration of injection. Three out of five patients did not feel any changes at the injection site, but another patient had severe pain, redness, and induration.

The exchange of information, a possibility of choosing the site of administration, and monitoring of the effects of treatment are all positive strategies that doctors and nurses can use to help patients in the compliance to the treatment with antipsychotic long-acting injections.

Key words: schizophrenia, antipsychotic long-acting injection, side effects

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INTRODUCTION

Schizophrenia is a mental disorder of the chronic course with exacerbations and remissions that lead to social and occupational disability, which makes it a disease of great public health importance, as it represents a burden both to the patient's family and to the community. Antipsychotics of the first and the second generation are the first line therapy in the treatment of schizophrenia. Patients' non-adherence to oral medication treatments is a potential problem that may lead to higher relapse rates which in turn worsen long-term outcomes and lead to poor prognosis (1).

Long-acting antipsychotics (fluphenazine, haloperidol) have been in clinical use since the 60s of the last century, while the second generation (risperidone and olanzapine) was developed in 2007. The importance of long-acting antipsychotics is reflected in the fact that almost half of the patients do not accept the treatment, which is why they are the drugs of choice in the treatment of non-complying patients. The most common reasons for rejecting the treatment with long-acting antipsychotics are pain at the site of application, leakage of small amounts of the drug into the subcutaneous tissue, which is the cause of irritation and lesions, even stigma and the obligation to go to hospital (2).

The use of long-acting injectable (LAI)-release formulations has the advantage of avoiding variability related to the absorption and effects of the first-pass metabolism which usually results in a better correlation between the dose and plasma levels concentrations relative to oral agents. Depot injections allow the use of the principle of the minimum effective dose, reducing the incidence of side effects and the risk of overdose. Long-acting antipsychotics may reduce medical costs and improve the quality of patient's life, as the frequency and the length of hospitalizations caused by acute exacerbations of the disease lessen (3, 4).

However, in spite of all the above mentioned benefits, the application of long-acting forms of antipsychotics is not so common, because of the development of the side effects like tardive dystonia or neuroleptic malignant syndrome (5). In addition, long-acting injections have been associated with a number of complications at the site of the injection including pain, nodules and indurations, muscle granulomas, fibrosis, abscess formation, and the accumulation of oil after repeated injections. The reason for these complications is the fact that depo formulations are traditionally manufactured as alcohols, which by esterification form highly hydrophobic esters that are only sparingly soluble in aqueous

fluids such as blood. These esters are dissolved in a variety of oils: sesame seed, coconut or other vegetable oil. Aqueous-based formulations generally have good injection site tolerability (6).

The four major sites for the administration of long-acting antipsychotics are the dorsogluteal site, ventrogluteal site, deltoid muscle, and vastus lateralis. Reporting studies cited the most common reasons for preferring the deltoid muscle site (expressed by >25% of patients) relative to others as easier, less embarrassing, faster, or less painful site compared to the gluteal site (7). The needle, which is used, must inject the medication into the muscle and not into the surrounding subcutaneous (fatty) tissue. A slower pace of introducing the needle is less painful for the patient, and the length and diameter of the needle have an important role in reducing the discomfort at the administration site, especially amongst women, who have more gluteal fat (6, 7).

Long-acting injections (LAI) are administered by mental health nurses, by primary care practice nurses, psychiatrists, and primary care doctors. Those who administer the injections need to be competent in the technical aspects of the procedure (8).

The main problems from the earlier research were the need for increased training and retraining of health personnel and patient involvement in the choice of treatment, as well as the need for clearer communication and information on long-acting injections for antipsychotic therapy.

Empowering patients and talking to the nurse and doctors were successful approaches to overcoming barriers to treatment with long-acting injectable antipsychotics, such as the fear of needles and weight gain (8, 9).

PATIENTS AND METHODS

The study included patients in the age group of 18 to 65 years, with equal distribution of males and females treated at the Clinic "Dr Laza Lazarević" and diagnosed with schizophrenia, and who had previously received at least two doses of depot injections. The study involved five patients who were treated with fluphenazine, haloperidol, risperidone given in the form of a long-acting depot injection, between November and December 2014, and four medical workers including doctors and nurses trained for the administration of depot injections. The data were collected by direct observation of preparation of a depot injection and observation of patients during injection administration. For the collection of data, a semi-structured interview "face to face" was also used, which contains 19 questions and is designed to last

for 15 to 30 minutes. Interviews were conducted in a relaxed atmosphere in the pleasant, cooled consulting room, where none of the patients was disturbed. All participants gave their written informed consent to participate in the study protocol that was conducted in accordance with the Declaration of Helsinki principles and was approved by the Ethical Committee of the Clinical for Psychiatric Disease, "Dr Laza Lazarević" in Belgrade. All potential participants were informed that the interviews were confidential and anonymous. Interviews were audio recorded, but for those patients who did not agree, the interviews were recorded in the form of notes. The important data sources were also case records of the participants that provided the past recorded observations and problems with the application of depot injections. The data were also collected from medical personnel who had been trained in the administration of injections, by direct observation of preparation and application of injections, and with the use of a semi-structured interview. The analysis identified meaningful segments which were further condensed these into the meaningful categories. The results were classified according to the Classification for Drug-related Problems (Pharmaceutical Care Network Europe Foundation). Methodology was conducted on the principle of based theories.

RESULTS

Two doctors, two nurses and five patients participated in the interview. The doctors did not administer long-acting injections. Both nurses had been working in the hospital for more than 30 years. Seven patients were recruited but two patients did not give their consent. In total, data of five patients were analyzed. Three patients were female, two were males, with age range 26–55 years. The analysis showed that problems of administration of antipsychotic long-acting injections could be condensed into nine categories in the interviews of medical workers and patients. The results were classified according to the Classification for Drug-related Problems V 6.2 (Pharmaceutical Care Network Europe Foundation) P 2.1- Adverse drug event (non-allergic).

Competence and training of the medical workers for LAI administration:

Doctors in these institutions did not attend the training for the administration of LAI. There was a training organized by pharmaceutical distributors of long-acting risperidone, but only for certain nurses who at that time worked at the Department of Polyclinic Psychiatric

Care. Both nurses had learned at school how to administer injections and had more than 30 years of practice. One nurse came later to the department and the other nurses helped her to get trained. "...representatives of pharmaceutical companies showed us how to unpack, prepare, administer, dissolve, shake and keep the injection..."

Sites and technique for the administration of LAIs:

Gluteal site, the upper outer quadrant, is the most popular site for administering LAIs. The nurses know that there is a needle for a deltoid injection, for Rispolept Consta®, but that needle is not used. Needles are packed in original packages. The doctor believes that the site of administration should be the patient's choice, however, the nurse is the one who decides. If the patient has an infiltration of the gluteal region, the deltoid muscle is used – but that rarely happens. Nurse No. 2 said: "...We would have to provide detailed information to the patient to explain what, why, how to use sites and techniques for the administration, but the question is whether they would be able to decide..." The needle used is a 0.8*40 for fluphenazine and haloperidol depot. The sting of the needle is deep, practically the whole needle is placed and injected slowly.

Registration of complications at the site of the injection application:

Patients report some side effects at the site of injections, but quite rarely. These side effects include nodules and indurations, muscle granulomas, fibrosis, abscess, pain, hardening after prolonged administration. The nurses tell the patients to report the problems they have to their doctor. Nurse No. 1 said: "... It happens that the medicine is not heated enough and then the patients feel more pain..." The doctor registers side effects if they are important for the functioning of patients. At the site of the injection, side effects appear rarely, it is predominantly a painful sensation. The doctor said: "...No allergies have been reported to this medicine so far...should there be an allergic reaction, the medicine would have to be excluded, but these are drugs that do not give a classic type of allergy...All other adverse effects are mild and have not been recorded..."

Three out of five patients did not feel the changes at the injection site. They did not have any problems with administration of LAI. In one patient, there was a mild pain and leg rigidity if the injection was administered several times in the same leg. Another patient had severe pain, redness, and induration. "...I have redness

and induration for a whole day, the next day they withdraw..." No one had allergy. These two patients massaged induration and put compresses, as advised by nurses. "...Nurses usually ask me if it hurts or not during the drug administration, if she should slow down..."

Care of patients and privacy:

All patients are provided with privacy in the intervention room, no one feels threatened. In the room for intervention there is just a nurse and a patient, even if someone enters there is was a cover. All patients have had communication with doctors and nurses. "...I am happy when the nurse and my doctor are there..."

Availability and evidence of LAI:

Long-acting risperidone is always available, shortages of fluphenazine and haloperidol are rare and patients are always notified in time. Each patient comes with an order for injection. The data on the patient, the doctor and the medicine are entered in the special protocol. The patient and the nurse sign the protocol.

Duration and frequency of treatment:

One of the participants had been treated with the LAI for less than 2 years, three for 5-7 years and one for over 10 years. Frequency of administration for patients who used fluphenazine and haloperidol depot was one month, and for risperidone two weeks.

Burden for the patients:

Three out of five patients feel burdened when they need to come to receive treatment, but all patients feel better after treatment and all patients always come regularly. "...It sometimes annoys me to come, sometimes a few days pass because I had no time to come ...because I go to faculty..." "...I have a lot of obligations. I have three men in the house, so it's hard to come..."

The choice of formulation therapy:

Most participants were able to identify advantages and disadvantages of the two formulations. Ease of use and avoiding forgetting to take tablets were repeatedly cited as advantages of LAIs. Advantages of oral medication cited by participants included privacy. Four out of five patients used tablets before they started using LAI, and they would never again return to per os use. "...I am protected then for an entire month, because injection drug is present in the blood throughout the month..."

Sense of stigma:

One patient regarded LAIs as being associated with stigma as evidenced by statements of the neighbors in the street who look at him differently. "...Sometimes I'm sad about it, sometimes I don't care..." Other patients did not have a sense of stigma, because they used LAI.

Analysis of the history of the disease of these five patients showed that notes and control examinations of patients were neatly evidenced. Any change in therapy was recorded, as well as worsening of the patient's condition as well as hospitalizations. The histories of the disease contain the laboratory report which includes basic biochemical analysis, lipid profile, prolactin and some drug concentration in the serum. In patients using risperidone, every control examination included weight-measuring. In the history of this patient was the explanation why this patient started using long-acting risperidone, e.g. because of hypersensitivity to typical antipsychotics, which leads to extrapyramidal syndrome. In one patient treated with haloperidol, metabolic side effects such as hypercholesterolaemia and dyslipidaemia were observed. However, no problem was recorded at the site of the injection application.

During the observation, it was noticed that patients cooperated well with nurses, and that they were satisfied with the effect of the therapy. Each patient received their own calendar with the date of the next control. Every patient was recorded through a special protocol. Two patients were observed to have abscess formations, but they did not want to take part in the interview. Two of them said that they felt pain at the site of the injection application. The patient did not permit a picture of the injection administration to be taken. The nurses were trained in the preparation and administration of injections. The administration lasted shortly. Before the application, nurses did not use any treatment to relax the patient.

DISCUSSION

This is a study which specifically investigates the attitudes of patients related to the administration of long acting injections in the treatment of schizophrenia. The objectives of this survey were to understand the factors driving LAI use as well as attitudes and preferences for different administration sites, formulation, frequency, and manner of administration. This analysis highlights that side effects, pain and unease at the administration site are all considered to be important factors when choos-

ing antipsychotic treatments for chronic schizophrenia patients and monitoring them. In interviews with nurses, we came to the conclusion that nurses who administer the injections are competent, and that the technical aspects and the application procedure have been learned at the training held by pharmaceutical distributors of long-acting risperidone. The patients who have been questioned are sure that the nurses administer these injections in a way that is virtually painless. Nurses decide on the sites of injection administration, and the most popular site is the upper quadrant of the gluteal muscle. Patients were not even given the choice. For the training programmes in the UK organized for nurses who administer LAI, they need to practice and have knowledge of psychopharmacology, anatomy and physiology of injection giving. All staff administering risperidone long-acting injection must have received training either from a qualified nurse who is competent in its administration or directly from the pharmaceutical company. This training is free and carried-out by the company representative. The nurse's experience and competence were checked and supervised by the monitor (10). Dorsogluteal site is the major site for the administration of LAIs except in the USA. Deltoid muscle is rarely used, as administering injection into this site causes more discomfort (11).

Another consideration in this discussion is that of needle length. Many authors have pointed out that the distance to reaching muscle is greater in the gluteal region, which is why longer than standard (longer than 50 mm) needle should be used, particularly for females, depending on body mass index (BMI) (12). Dimensions of the needle which is used were 0,8*40 for haldol® and fluphenazine depot, whereas dimensions for Rispolept-Consta® were in the original pack. Not enough attention is paid to the choice of the needle diameter, just the currently available ones are used.

In a Swiss study, two-thirds of patients with schizophrenia reported that they had not received sufficient amount of information about the availability of depot antipsychotics from their psychiatrist (13). In England in 2007, only 43% of patients stated that they could make decisions about the medication they take; only half of the patients were informed about the purpose of new medication formulation medication before it was started, and fewer than 40% reported that they had been told about potential side-effects (12). In our research, we came to the conclusion that psychiatrists did not give comprehensive information about the choice of medications, including formulations, application site, and adverse effects.

Three of five patients did not have any problems with the administration of LAI. Two patients had indurations, but they did not accept to participate in the interview. During the observation of the medical documents, it was concluded that monitoring of side-effects was not extensive and that doctors did not write adverse effect and did not care about subjective feeling like pain, which is the most common side-effect. In terms of beliefs about LAIs, injection pain and fear of needles were raised as a downside of LAIs. Pain at the injection site is the most common injection site complication of LAIs (14). One patient perceived LAIs as being associated with stigma, in particular that receiving a LAI would lead others to think that their illness was severe. The results highlight the importance of providing patients with accurate information about treatment options and efforts of mental health organization to combat stigma, particularly in patients with first-episode psychosis (15). The patients who had used tablets before they started using LAI would never return to the oral use, reporting an ease of use and more free time. In a Spain, study patients treated with LAI risperidone showed better performance in their habitual social activities and compliance than patients treated with risperidone plus oral second-generation antipsychotics (16).

Its overall negative perception could be reduced if psychiatrists were to provide broader and more comprehensive information to patients with schizophrenia and their relatives. The reasons for insufficient commitment of physicians and nurses are the lack of time, five psychiatrists in this Department of Polyclinic Psychiatric Care, 600-700 patients per week, and lack of motivation.

CONCLUSION

LAI antipsychotics are truly superior to their oral equivalents in the prevention of relapse and hospitalization in patients with schizophrenia and it is important that psychiatrists communicate their views and convince their patients about the benefits of these formulations. Exchanging information, making better choices about the administration site, and monitoring the effects of treatment are all positive strategies that doctors and nurses can use to help patients in the compliance to the treatment. Following administration, it is important to observe the patients for immediate adverse effects and injection site reactions. Monitoring side-effects requires both objective observation and reporting.

The availability of a deltoid administration, besides the gluteal region, offers additional opportunity in

the mode of LAI antipsychotic administration and patients should be given a choice of the drug's application site.

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Problemi u primeni antipsihotika u obliku depo preparata u lečenju shizofrenije

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SAŽETAK

Cilj ovog istraživanja bio je ispitivanje problema kod primene antipsihotika u obliku depo preparata u lečenju shizofrenije. Pored mnogih prednosti, dugodelujuće injekcije antipsihotika su povezane sa brojnim komplikacijama na mestu primene.

U kvalitativnoj studiji učestvovala su četiri medicinska radnika i pet bolesnika na terapiji lekovima: flufenazin, haloperidol i risperidon dati u obliku depo injekcija. Podaci su prikupljeni direktnim posmatranjem, analizom istorija bolesti i semistrukturiranim intervjuom.

Analizirajući intervjue bolesnika, psihijataru i medicinskih sestara dobijeni rezultati su podeljeni u devet ključnih kategorija: kompetencija i obučenosť medicinskih radnika, mesto i tehnika primene injekcija, praćenje komplikacija i neželjenih dejstava, briga o bolesniku i njegovoj privatnosti, dostupnost i evidentiranje terapije, trajanje i učestalost tretmana, opterećenje bolesnika, izbor formulacije terapije i prisustvo osećaja stigme.

Praćenje neželjenih efekata antipsihotika u obliku depo preparata se ne vrši u dovoljnom obimu, kao ni evidencija od strane lekara. Medicinske sestre su obučene za davanje dugodelujućih injekcija. Nedovoljno pažnje se posvećuje izboru prečnika igle, a pacijentu nije data mogućnosť da izabere mesto ubrizgavanja leka. Promene na mestu primene leka nisu imala tri od pet pacijenata, dok su kod preostalih bili prisutni jaki bolovi, crvenilo i induracija.

Razmena informacija, mogućnosť izbora mesta primene leka i praćenje neželjenih dejstava predstavljaju pozitivne strategije koje lekari i medicinske sestre treba da koriste da bi komplijantnosť bolesnika bila bolja tokom primene dugodelujućih injekcija antipsihotika.

Ključne reči: shizofrenija, dugodelujuće injekcije antipsihotika, neželjena dejstva