

Adherence and Long-Acting Injectable Antipsychotics in Schizophrenia: An Update

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ABSTRACT

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Nonadherence to antipsychotics poses a major problem in the long-term management of schizophrenia. Subjective measures of adherence (self-reports, provider reports) are unreliable, more objective methods (e.g., electronic monitoring, plasma levels) are neither available in clinical practice, nor are they infallible. Risk factors include history of nonadherence, substance use, limited insight, treatment with antidepressants, medication-induced cognitive impairment, hostility, and violent behavior. Nonadherence results in partial or no response to antipsychotic treatment with many adverse consequences, including higher mortality. A recent meta-analysis somewhat surprisingly failed to prove higher adherence to long-acting injectable antipsychotics (LAI) than to oral antipsychotics. However, unexpectedly high adherence in the reviewed trials suggests selection bias. This is further supported indirectly by the findings from two large observational studies from Finland. They showed that LAI, as compared to oral formulations of the same drugs, were associated with a significantly lower risk of rehospitalization and drug discontinuation. Prescription data from the Czech Republic indicate that LAI are underutilized. Contrary to traditional assumptions, patients with previous exposure to LAI appraised them favorably and frequently preferred them in the long-term treatment. LAI may be considered not only for nonadherent, relapsing or difficult-to-manage patients, but also for actively participating, well-informed patients with insight.

Key words: Adherence, long-acting injections, antipsychotics, schizophrenia

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INTRODUCTION

The effectiveness of any treatment depends on three principal factors: efficacy, adverse effects, and adherence. The first two factors (efficacy and adverse effects) have been the focus of medical reasoning for decades. Adherence has been recently receiving increased attention in the pharmacological treatment of medical conditions such as diabetes and hypertension, as well as psychiatric disorders such as schizophrenia, bipolar disorder, and depression.

Nonadherence to antipsychotic treatment is a major problem in the management of schizophrenia. Depending on the ascertainment methods, approximately 40-50% of schizophrenia patients are nonadherent (1,2), and 50-55% of hospital admissions are attributable to nonadherence to medication (1).

Guidelines recommend regular adherence monitoring (2), but it is frequently overlooked in overcrowded hospitals and busy outpatient facilities. This is not surprising since most monitoring methods require having sufficient time to talk with the patient

and/or his family.

The introduction of antipsychotic depot formulations raised hopes that a technological solution to the problem of nonadherence was at hand. Surprisingly, demonstrating the effect of depot formulations on adherence turned out to be less straightforward than expected.

In this review, we define nonadherence, examine methods for its assessment, assess causative factors, and appraise its impact on outcomes of schizophrenia. We also review the role of long-acting injectable antipsychotics (LAI), also referred to as 'depot formulations'. The review is an expanded and updated version of an article that was published in Czech in 2011 (3).

Terminology and Definitions

Adherence to treatment is defined as the extent to which the patient's behavior conforms to recommendations provided by a health care provider. Compliance is defined in the same way, but this term

implies a passive acceptance of treatment recommendations (1) and therefore it has been gradually replaced by adherence which has a more neutral connotation with respect to the patient's attitude. Persistence may be defined as continuously refilling prescriptions in accordance with the suggested duration of therapy (4). Patients may be persistent in refilling prescriptions and receiving medications, but at the same time they may be nonadherent to treatment when they do not use the received medication as prescribed. Retention is typically defined as "time to study drug discontinuation" (5). It thus corresponds to the persistence with treatment used as an outcome measure in recent schizophrenia trials the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (6) and the European First Episode Schizophrenia Trial (EUFEST) (7). Moreover, the term retention is used more broadly as time when patient receives any treatment, including nonpharmacological interventions.

Nonadherence to pharmacological treatment can be subdivided into two major classes: complete cessation of medication, and partial nonadherence. It is the second class that presents definition problems. An expert consensus statement endorsed the percentage of medication not taken over a period of time as the preferred definition of nonadherence (2). The experts agreed that patients taking at least 80% of prescribed medication may be considered fully adherent, those taking 50-79% are partially adherent, and those taking less than 50% are nonadherent. Medication gaps, described as specific contiguous time periods off medication during a certain interval ("drug holidays"), were also endorsed as a possible definition of nonadherence. The experts agreed that a medication gap of at least one week during a period of 3 months should be considered as an adequate definition of nonadherence (2).

Several measures of adherence were created for studies of pharmacy refills; the Medication Possession Ratio (MPR) is the one most frequently used. MPR is the ratio of the amount of medication the patient received (prescriptions filled) to the amount of medication needed to receive in order to take the medication continuously as prescribed. MPR close to 1.0 (80-110%) is considered to define good adherence (8).

Assessment Methods

Adherence to oral medication can be assessed by subjective methods such as patient self-report, significant other report, provider report, or chart review, or objective methods such as pill count, monitoring of pharmacy refills, Medication Event Monitoring Systems (MEMS) in which the opening of the pill bottle is electronically recorded, and blood or urine medication level testing. Patient self-report and provider report are the most frequently used method to assess adherence in research studies (9) and in clinical practice.

Nurses' rating of patient adherence and attitude towards medication treatment on a 7-point scale is the basis of Hayward scale (10) that was used for example in the EUFEST trial (7).

None of these methods are perfect, and there is no "gold standard". Pill counts may be consistent with the prescribed consumption, but there is no way of knowing whether the patient actually consumed all the pills that are missing at the count. A similar problem may occur with MEMS. Patients may consume medication only for the two or three days before scheduled blood or urine samplings ("white coat compliance"). The results showing plasma levels in the expected range may then give an erroneous impression of continued adherence. On the other hand, considerable interindividual differences in metabolism of antipsychotics and other medications exist. Very low or even undetectable plasma levels of medications can therefore be found in fast metabolizers who may be fully adherent to their medication regimen. In these rare cases, the results may give an erroneous impression of nonadherence.

Nevertheless, some authors use plasma levels to assess adherence. A comparison of self-reported adherence with plasma levels of medication in 135 schizophrenia patients has demonstrated an overestimate of adherence by self-reports (11). A similar inflation of adherence estimate by self-report in comparison with pill count and MEMS has also been reported (12). The latter two measures were correlated with each other. Physician's estimates of adherence showed low correlations with other measures, suggesting their low validity.

Thus, in summary, the most frequently used methods to assess adherence (self-report and provider report) are not reliable, and self-report may overestimate adherence. These problems have implications for research and clinical practice.

Causes, Correlates, and Predictors of Nonadherence

Willingness and ability to take medication as prescribed are necessary preconditions for adherence. Patient's willingness can be reduced if he thinks he does not need the medication, has limited insight into mental illness, if the medication has adverse effects (such as parkinsonism, weight gain, or loss of libido) or if it is not effective, and if the therapeutic alliance between the patient and his doctor is poor. Lack of family support for the treatment will also undermine patient's willingness to take medication.

Emerging evidence suggests that rising hostility may also reduce patient's willingness to take medication as prescribed (13). However, rising hostility itself may be the result of inadequate treatment or inadequate antipsychotic response, which in turn leads to nonadherence. Relationship between hostility and nonadherence has been replicated in a re-analysis of data from the EUFEST trial (14).

Ability to take medication may be reduced by cognitive impairment or depression. Ability to obtain medication may be constrained by financial problems and logistic difficulties such as poor access to a remote pharmacy for patients without a car. Comorbid substance use disorders (15) and homelessness are associated with poor adherence to antipsychotic treatment.

A prospective study of 1579 patients with schizophrenia aimed to identify predictors of nonadherence (16). Adherence with any oral antipsychotic medication was assessed using patient self-reports and medical record prescription information. The best single predictor of future nonadherence was nonadherence during the 6 months prior to enrollment (odds ratio = 4.1, 95% confidence interval = 3.1 to 5.6, $p < 0.001$). The best set of predictors of nonadherence

included prior non-adherence, recent illicit drug use, recent alcohol use, prior treatment with antidepressants, and greater patient-reported, medication-related cognitive impairment (16). We note that history of violent behavior and incarceration were also significantly more frequent in nonadherent patients. Taken together with the data on alcohol and illicit drug use mentioned above, this suggests that nonadherence in schizophrenia patients may be in part engendered by a comorbid personality disorder. Similar results were yielded by a Norwegian study examining adherence among 154 patients by serum concentrations (17). Nonadherent patients had higher rates of illicit substances and alcohol use, poor insight, but did better than adherent patients in measures of cognitive functioning.

Psychosocial Interventions Targeting Nonadherence

Various approaches aiming to improve adherence are available. They may utilize the roles of care providers, physicians, nursing staff, pharmacists, patients, their families, manufacturers, or media. As mentioned previously, adherence is lower if the patient does not believe in the need of treatment, has poor insight, or does not have a family support. These specific problems can be addressed by psychosocial interventions. Systematic psychoeducation of the patients and families answers questions concerning medication, its benefits and risks, emphasizes the need of close collaboration with mental health professionals and other care providers.

Methods trying to improve insight into illness include cognitive behavioral therapy and remediation (18). However, the results of specific "compliance therapy" utilizing principles of cognitive behavioral therapy are equivocal. Whereas in a small uncontrolled study with schizophrenia and schizoaffective patients compliance therapy failed to yield positive findings (19), in a randomized controlled trial with 47 schizophrenia patients compliance therapy was superior to nonspecific intervention (10). Odds ratio to meet criteria of compliance in active group was 5.2 (95% CI, 1.5, 18.3). Therapeutic effect lasted over the next six

months. The importance of work and collaboration with family is often underestimated, despite the fact that they are promoted in the general guidelines addressing nonadherence problem (2).

Consequences of Nonadherence

The most obvious consequence of nonadherence is partial or no response to treatment. This was demonstrated prospectively in an 8-week study of 599 patients diagnosed with schizophrenia or schizoaffective disorder (13). Adherence was assessed by pill count. Nonadherent patients had significantly less improvement on the PANSS scale, and longer duration of nonadherence reduced the likelihood of response.

In the longer term, nonadherence increases the risk of relapse and consequent rehospitalization. A study using pharmacy refill claims in 4325 schizophrenia patients evaluated the relationship between adherence to antipsychotic medication and risk of hospitalization (20). Nonadherence was estimated by using four different measures: gaps in medication therapy, medication consistency and persistence, and MPR. Patients were followed for one year. Risk of hospitalization was significantly correlated with all measures of nonadherence. The longer medication-free intervals led to higher probability of rehospitalization.

Using a prospective design and rigorous yet nuanced definitions of nonadherence, a recent study demonstrated that relatively short periods (2-4 weeks) of partial nonadherence elevate the risk for exacerbation of symptoms or relapse in patients in early stages of schizophrenia (21).

Analysis of pharmacy data in a cohort of 67079 schizophrenia outpatients revealed that patients with MPR around 1.0 had the lowest rates of admission (8). Increased risk of hospitalization was observed not only in poorly adherent patients (MPR below 80%), but also in those receiving excess antipsychotic medication (MPR above 110%). Thus, either failing to refill or stockpiling meds may be indicators of unreliable pattern of compliance with treatment regime.

Inadequate or lacking antipsychotic treatment can arise from nonadherence, nonpersistence, or failure to

prescribe. Lack of treatment is associated with elevated mortality in patients with schizophrenia. This was demonstrated in a study comparing the mortality in 66881 Finnish patients with schizophrenia with the total population of Finland and linking these data with the use of antipsychotic drugs (22). Long-term cumulative exposure (7-11 years) to any antipsychotic treatment was associated with lower mortality than was no drug use (hazard ratio 0.81, 0.77-0.84). In patients with one or more filled prescription for an antipsychotic drug, mortality decreased with increasing cumulative drug use. Clozapine was associated with a substantially lower mortality rate than other antipsychotics. Higher mortality in schizophrenia patients using no antipsychotic in comparison with those using any antipsychotic was recently observed in another Finnish cohort (23).

Covert nonadherence may affect research and clinical management. Dosing regimens proposed for newly introduced medications are based on studies that may not have adequately controlled adherence, and thus may be faulty. In clinical practice, providers frequently do not have adequate information on adherence. Lack of response to treatment may be due to ineffectiveness of the treatment itself, or to non-adherence. If non-adherence is not recognized as the cause of non-response, clinician may mistakenly prescribe higher doses or add other medications, neither of which the patient will take, having been nonadherent all along.

Schizophrenia patients' families, health care systems, and society are affected by nonadherence to antipsychotic treatment. Families are in the unwelcome role of constantly supervising and persuading the patient to take medication. Health care systems and society in general are faced with increased direct medical costs due to emergency treatments and hospitalizations required for nonadherent patients. There are also increased indirect costs due to lack of productivity of undertreated patients. Finally, nonadherence to antipsychotic treatment increases risk of violence and victimization. This results not only in health risks for victims and perpetrators, but also increased costs for the criminal justice systems.

Adherence and Persistence with Oral Antipsychotics

Adherence to second generation antipsychotics (SGA) was significantly higher than to the first generation antipsychotics (FGA) in a study using prescription refill review (24), but not in another much larger study using the same method (25) or in another study using MEMS (26).

Persistence (or lack of it) was measured in the CATIE trial (6) as the time to discontinuation of treatment for any cause. In Phase 1 of the CATIE, that time was longer in patients receiving olanzapine than in those on quetiapine, risperidone, perphenazine, and ziprasidone; the superiority of olanzapine over quetiapine and risperidone reached the level of statistical significance. Amisulpride, haloperidol, olanzapine, quetiapine, and ziprasidone were compared for persistence on treatment (as time to discontinuation) in the EUFEST study (7). Olanzapine was associated with the highest persistence. Clozapine showed superior persistence on treatment compared to other antipsychotics in observational studies (4, 27).

Long-Acting Injectable Antipsychotics (Depot Formulations)

Effects of LAI on adherence, persistence, relapse, and rehospitalizations

The introduction of SGA had raised hopes that problems with nonadherence to treatment would be alleviated because of the lower burden of side effects such as parkinsonism with these newer medications. However, as reviewed above, this did not happen. The introduction of depot formulations of antipsychotics raised similar expectations since it would certainly eliminate covert nonadherence, and overt nonadherence would become immediately obvious to the caregivers. However, the results of randomized controlled trials (RCT) comparing adherence with long-acting injectable antipsychotics versus oral formulations have not demonstrated the expected superiority of the depot. A recent meta-analysis of such studies has found no

significant difference in adherence between depot and oral formulations of antipsychotics in published trials of schizophrenia patients (28).

However, the RCT included in the meta-analysis have many limitations. The trials were implemented at different time periods, using different methods. One trial compared LAI risperidone with oral quetiapine, thus conflating the effects of difference between drugs with difference between formulations. Importantly, the subjects selected for these studies appeared to be unusually adherent. In 5 studies comparing adherence in LAI and oral formulations of antipsychotics, there were only 55 nonadherent patients out of the total of 574 schizophrenia patients receiving oral formulations. Thus, instead of the expected 40-50% of nonadherent patients (1), the rate was less than 10%. It would appear that there was a selection bias favoring adherent patients, or that the trials were conducted under environmental conditions that strongly enhance adherence. In such circumstances, a putative effect of LAI on adherence could not be detected (i.e., there was a floor effect). Thus, in summary, the lack of evidence for a beneficial effect of LAI on adherence is very far from evidence for a lack of such effect. Studies selecting subjects for low baseline adherence remain to be done.

As discussed above, relapse is among the most important consequences of nonadherence to antipsychotic medication. A meta-analysis of 10 studies involving 1672 schizophrenia patients has demonstrated a significant superiority of depot versus oral preparations in preventing relapse (risk ratio 0.70, 0.57- 0.87) (28). The mechanism of the effect of LAI on relapse in RCT is not clear. Several of the studies used for the analysis of relapse were also used for the analysis of adherence in the Leucht paper (28). If the effect on relapse was mediated by an effect on adherence, one would expect that that comparison of data on relapse with those on adherence of the Leucht paper would show that studies favoring depot on adherence would also favor depot in terms of relapse reduction. However, scrutiny of the presented data does not support such a notion.

Several additional randomized studies that were not included in the Leucht meta-analysis yielded important, though mostly negative, data. In a sample of 335

patients, depot risperidone and oral aripiprazole did not differ in loss of retention, time in remission, or time to relapse (29). LAI risperidone failed to be more effective than oral antipsychotics in prevention of hospitalization among 369 patients (30). Similarly, LAI olanzapine pamoate was as effective as oral olanzapine in time and number of treatment discontinuation and relapse prevention in a sample of 525 stabilized outpatients (31). In a small open, randomized 54-week study with 37 first-episode patients LAI risperidone indicated initial superiority in adherence over oral risperidone at 12 weeks, but the difference was lost at the endpoint (32).

Positive results were found in an international postmarketing observational trial with long-acting injectable risperidone, eSTAR (electronic Schizophrenia Treatment Adherence Registry) (33). Summary of two-year results from six countries based on data from 1659 patients showed a high persistence with depot risperidone, up to 85% (33).

Two-year analysis of a subsample of 1308 Czech and Slovak patients enrolled in eSTAR confirmed high persistence with long-acting risperidone injections: 76.4% in the Czech Republic and 87.8% in Slovakia (34). The number of patients in remission increased from 2.8%, respective 2.9% at baseline to 47.4% (Czech Republic), respective 29% (Slovakia) at two-year follow-up.

The Spanish subsample of eSTAR was analyzed as an open nonrandomized prospective comparison of retention on depot risperidone (N=1345) versus oral antipsychotics (N=277), mostly olanzapine or risperidone (35). LAI treatment was associated with higher persistence with treatment (81.8% vs. 63.4%; $p < 0.0001$) and greater reduction of CGI scores (-1.14 vs. -0.94; $p = 0.0165$).

Data from the 3-year, prospective, observational Schizophrenia Outpatient Health Outcome study compared the effectiveness (treatment discontinuation and hospitalization) of depot and oral typical antipsychotics in nonadherent outpatients with schizophrenia (36). Of 1642 nonadherent patients, 431 (26%) started an oral typical ($n = 169$) or depot typical ($n = 262$) antipsychotic and were included in the analysis. Treatment discontinuation was significantly lower in

the depot typical cohort (hazard ratio: 0.72, 95% confidence interval: 0.54-0.97, $P < 0.05$). Younger age and more severe positive symptoms were also associated with higher discontinuation. The frequency of hospitalization and the mean number of hospitalizations were both significantly lower for the depot typical cohort at 6 months ($p < 0.05$) compared with oral typicals (36).

Discontinuation of treatment for any cause and rehospitalizations were studied in 2230 adult patients in community care after the first hospitalization for schizophrenia or schizoaffective disorder in Finland (27). Patients were followed up for an average of 3.6 years. Number of patients who discontinued their initial treatment (treatment that was started within 30 days after first discharge) can be seen as a measure of persistence for that treatment. FGA and SGA were included among the treatments.

Relative risk (RR) for discontinuation was calculated for each treatment with oral haloperidol as the comparator treatment. Highest persistence (lowest discontinuation rate during the follow-up period) was observed with clozapine (RR=0.17; 0.10 - 0.29), followed by depot perphenazine (RR=0.24; 0.13 - 0.47). The risk for discontinuation for oral perphenazine was similar to oral haloperidol (RR=0.92; 0.58 - 1.46), and significantly higher than for depot perphenazine. Analogous calculations of RR were performed for rehospitalizations. Depot perphenazine showed the lowest RR of all treatments examined. It was significantly superior to oral perphenazine.

A recent study using a different cohort of Finnish patients (N=2588) focused particularly on the comparison of depot and oral formulations of the same antipsychotics (23). Similar to the previous study by the Tiihonen group described above (27), the risk of rehospitalization and drug discontinuation in a nationwide cohort of patients hospitalized for the first time with a diagnosis of schizophrenia. In a pairwise comparison between LAI and their equivalent oral formulations, the risk of rehospitalization for patients receiving LAI was about significantly smaller than that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI=0.17-0.75). In analogous pairwise

comparison. the risk for discontinuation for any cause in patients receiving depot versus patients receiving oral formulation was 0.41, 95% CI = 0.27–0.61). Compared with oral risperidone, clozapine and olanzapine were each associated with a significantly lower rehospitalization risk.

Thus, these observational studies demonstrated superiority of a depot over oral formulation for persistence with treatment and for prevention of rehospitalizations.

In a study focusing on the continuity of care, schizophrenia patients who had been receiving LAI before hospitalization were more likely to show up for their first outpatient appointment within thirty days than those receiving oral preparations or no antipsychotics (37). This finding remains unexplained. Trying to integrate it with the reports of superior persistence on treatment with clozapine and with LAI, we observe that these findings have one thing in common: patient's face-to-face contact with health care personnel is required on a regular basis for injections of depot medications or for blood draws for white blood cell counts. We speculate that over a period of time, these contacts facilitate the development of a therapeutic alliance between the patient and his care givers. It is possible that the effects of such alliance carry over even after an interruption of regular contact by hospitalization or other factors, and that it is conducive to persistence on treatment.

Patients' perception of LAI antipsychotics

One of the traditionally cited hurdles preventing from wider use of LAI in clinical practice is their negative image among the consumers, patients and their families. There is a popular assumption that LAI are associated with more severe and less-manageable side effects, plus, more importantly, arguably compromise individual decision autonomy and involve an element of coercion (38).

However, available data challenges the presumed prejudices on patients' part and offers more plastic picture. A systematic review of patient attitudes to depot antipsychotic scrutinized all published reports

(39). Literature search yielded 18 studies examining patients' perception and/or subjective satisfaction with LAI. Their quality varied greatly and the samples' representativeness of the clinical populations was questionable. Nevertheless, the review conclusions suggested that patients may hold a favorable opinion on depot injections. As for the attitudinal or preferential data, ten out of twelve reports included positive views on LAI, one negative and one neutral attitude. Direct comparison of preference of oral vs. depot medication showed somewhat unexpectedly that patients in five out six studies preferred to receive LAI over oral tablet. A single report of patients switched from depot antipsychotics to oral risperidone found that patients preferred oral administration (40). A follow-up review identified additional studies assessing patient preference (41). Out of five reports published between 2001 and 2008, one conveyed patients' positive appreciation of LAI, two neutral, and two negative. Preference for LAI increased with familiarity or duration of exposure. It is likely that exposure to depot formula enhances its acceptance, as corroborated by a pre-discharge survey of 300 patients from nine psychiatric hospitals in Germany (42). One-hundred and forty-five patients were naive to depot treatment, 95 had experienced depot earlier and 60 were currently on depot medication. Acceptance of LAI was 73% in patients currently on depot, 45% in patients with previous experience with depot, and 23% in depot-naive patients.

Perception of LAI may vary across geographical regions. This is possibly confounded by different historical and cultural background, as evidenced by two European examples. A small study from a Swedish community mental health setting showed that patients on LAI appreciated positively a control over psychotic symptoms they had experienced during previous episodes (43). The second example comes from Switzerland, the country with the arguably lowest rates of LAI use in Europe (5%). Among three study groups (patients, psychiatrists, and relatives), the most favorable view of depot formulation was held by the relatives (44). Patients without LAI experience reported that their psychiatrists did not recommend change to depot (91%) and even failed to inform them about this option (79%).

Psychiatrists' perception of LAI antipsychotics

A systematic review of studies evaluating attitudes of mental health professionals towards LAI identified eight relevant reports (45). In summary, depot formulas were considered to be (a) old-fashioned, (b) stigmatizing, (c) causing more side effects, (d) costly, and (e) not prescribed because of a presumed adherence to oral medication. An example of the reviewed studies is a cross-sectional survey among 143 psychiatrists from the UK (46). Whereas a substantial proportion of them believed that LAI were as efficacious as oral antipsychotics (91%), enhanced compliance (81%), prevented relapses (94%), at the same time depot were considered to be old-fashioned (40%), stigmatizing (48%) and inducing more side effects than oral drugs (38%). However, psychiatrists' attitudes and stereotypes may be changing over time, a similar survey five years later found that the perception of LAI was more favorable, although at the same time their prescription was declining (47). Similarly to the patients' perception, positive attitudes of staff correlated closely with the extent of their knowledge (41).

A series of surveys on the acceptance of LAI has been completed by a German group. Heres with collaborators (48) questioned 350 psychiatrists attending international congress of biological psychiatry (though nearly all respondents were German psychiatrists) on their reasons not to prescribe LAI. The most cited reason for all depot antipsychotics was presumed compliance with oral drug. First-generation LAI would not be prescribed due to the high risk of EPS, patients' refusal, reluctance to use them in first-episode patients or after a relapse, or fear of poorer control of effect compared to oral drug. Second-generation LAI would not be given because of patients' refusal, they would not be appropriate after relapse, due to high costs, or the needed drug was not available in a depot form.

Psychiatrists themselves prefer LAI over oral medication in relapse prevention if there is a minimum of 10% and higher difference in absolute risk for a relapse favoring depot (49). There might be also a shift in the psychiatrists' view on the use of LAI in first-episode patients (50). A survey among 198 psychiatrists concluded

that the principal objections were seen on the part of drugs (limited availability of the second-generation antipsychotics in depot form) or patients (first-episode patients frequently refuse LAI, patients underestimate risk of a relapse after first episode).

A multidimensional and cluster analysis based on a questionnaire of 248 psychiatrists helped to identify two patient subgroups that may most benefit from LAI (51). The first, 'traditional' group consisted of patients with previous relapses, history of non-compliance, who posed a hazard to others and were at risk of suicide. However, the second group was vastly different, consisting of patients well-informed about their illness, with high education, open to antipsychotic treatment, with high level of insight, good therapeutic alliance, and high level of participation in decisions. These two distinct subgroups perfectly illustrate the shift in psychiatrists' perception of the LAI in the long-term treatment of schizophrenia.

Thus, it is of no surprise that there have been first clinical trials with the administration of LAI in young patients during early phases of illness (52), or even first-episode patients (32, 53). In the study by Emsley and collaborators (53), fifty newly diagnosed patients with schizophrenia or schizophreniform disorder were administered LAI risperidone. Two-year treatment was completed by 36 patients (72%); 78% of them achieved 50% symptom reduction, 64% were in remission and 4 relapsed. Following study completion, 33 patients opted to discontinue LAI treatment and subsequently 79% of them suffered from relapse; median time to relapse was 163 days (54).

Availability and utilization of LAI antipsychotics in the Czech Republic and in the Slovak Republic

Depot antipsychotic formulations were widely used in Czechoslovakia in the past; some of them were even original compounds developed here. Nevertheless, available data indicates their continuing underutilization. In 2010, LAI made up mere 10.7% of the total prescription of all antipsychotics in the Czech Republic (IMS Health data). The most frequently prescribed was depot haloperidol (39% of all depot formulations),

followed by fluanxol depot (20%), flupenthixol depot (17%), zuclopenthixol acetate (12%), and long-acting risperidone (13%). In Slovakia, LAI as of 2010 made up to 10% of all prescribed antipsychotics, the most frequently used were zuclopenthixol acetate and risperidone microsphere (both 29%), then flupenthixol (21%) and haloperidol depot (20%). Olanzapine LAI newly available from 2010 took just 0.1% share of the depot market.

The major limitations preventing wider use of depot formulas of atypical antipsychotics (risperidone, paliperidone, and olanzapine) in many countries, including the Czech Republic and Slovakia are still mainly economic barriers such as prescription and reimbursement limits.

CONCLUSIONS

There is a general agreement that nonadherence to antipsychotic medication poses a major problem in the long-term management of schizophrenia. Currently, there are no reliable methods to measure adherence. The most frequently used self-reports and provider reports may inflate the rates of adherence. More objective assessments (electronic pill count, plasma levels) are too expensive in everyday clinical practice plus they are not completely infallible.

Factors associated with poor adherence are history of nonadherence, recent substance use, limited insight, prior treatment with antidepressants, cognitive impairment (sometimes induced by medication), current hostility, and history of violent behavior. It may thus be assumed that timely recognition and treatment of comorbid conditions (substance abuse, depressive symptoms) together with better tolerated antipsychotics might improve cooperation with treatment regimen.

Nonadherence results in partial or no response to antipsychotic treatment with all negative consequences, including higher mortality. The high rates of nonadherence among schizophrenia patients imply that without adequate control for adherence it is virtually impossible to tell in nonresponders whether the prescribed medication is not working due to lack of efficacy or simply because is not taken.

The obvious solution to this problem would be the use of depot antipsychotics. Nevertheless, a recently published meta-analysis comparing adherence to oral and LAI failed to confirm superiority of depot formulations. It should be noted that the analyzed studies reported unusually high rates of adherence, thus the results must be viewed with caution and considered as inconclusive at best. Indirect and replicated evidence comes from large observational studies. Two cohort studies in Finland showed that depot formulation as compared to oral formulation of the same antipsychotic was associated with a significantly lower risk of rehospitalization and drug discontinuation. Similar results were seen in a large observational study.

LAI are underutilized. Their refusal by patients plus psychiatrists' prejudices were traditionally blamed. However, surveys repeatedly showed that patients with previous exposure to LAI appraised them more favorably than those with no experience or little information. Upcoming availability of the second-generation antipsychotics in depot formulation may also contribute to the shift in the psychiatrists' attitudes. In addition to the use of LAI in nonadherent, frequently relapsing patients with a history/current risk of harm to themselves or others, administration of LAI in a different patient population is considered. Actively participating, cooperative, well-informed and educated patients with insight may also benefit from depot antipsychotic treatment.

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