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Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry

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Abstract

Objective: As psychopathology and social functioning can worsen with repeated psychotic episodes in schizophrenia, relapse prevention is critical. Because high nonadherence rates limit the efficacy of pharmacotherapy, the use of long-acting injectable (LAI) antipsychotics is considered an important treatment option. To date, many studies comparing LAIs and oral antipsychotics have been conducted; however, the results are mixed, and careful interpretation of the data is required.

Study Design and Setting: Selective review of existing literature regarding LAIs. We especially focused the discussion on the impact of the design of studies with different approaches comparing LAIs and oral antipsychotics in preventing relapse.

Result: The results were diverse and were influenced by the design used, that is, randomized controlled trials (RCTs) showed LAIs and oral antipsychotics to have similar effects, whereas mirror-image and some large cohort studies showed LAIs to be superior to oral antipsychotics.

Conclusion: Divergent results from studies using different methodologies create a dilemma for comparative effectiveness research, and LAI studies may serve as an example of a situation in which a conventional RCT is not the gold standard. Traditional RCTs generally increase adherence compared with clinical practice and, therefore, might not be well suited to detect differences between LAIs and oral medications, because any increase in adherence affects patients on oral medications more than those on LAIs and thus leads to an underestimation of any potential difference in effectiveness. A possible solution would be the implementation of a true effectiveness trial in which post-randomization involvement would be kept to a minimum to better reflect routine practice.

Keywords: Schizophrenia; Antipsychotics; Long-acting injection; Depot; Randomized controlled study; Mirror-image study

1. Introduction

Improving the course and outcome of psychiatric illness often involves the use of medications to prevent recurrence of acute illness. In the case of a condition such as schizophrenia, an enormous number of randomized controlled trials (RCTs) have been conducted demonstrating the value

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What is new?

Key findings

- The results of the LAI studies differ considerably depending on the design, for example, randomized controlled trials (RCTs), mirror-image studies, and naturalistic cohort studies.

What this adds to what was known?

- It is important to summarize the findings of different types of studies to provide a framework for discussions about the appropriate methodology.

What is the implication and what should change now?

- The traditional RCT is not necessarily the gold standard for examining the effectiveness of LAIs.
- Future RCTs may benefit from including patients at high risk for relapse and those most closely reflecting routine clinical care. In addition, a true large simple trial might be most informative.

of antipsychotic medications in the reduction of acute signs and symptoms as well as the prevention of recurrence of acute exacerbations. These effects are as dramatic as those of many other widely accepted treatments in general medicine [1]. Patient adherence/compliance in taking prescribed medications is one of the most challenging aspects of health care [2]. This pertains both to full nonadherence and to partial nonadherence, which may be even more common. Numerous studies of schizophrenia have shown nonadherence to be a frequent problem and a common cause of relapse, rehospitalization, and the loss of hard-won gains in psychosocial and vocational adjustment [3]. At the same time, it has been demonstrated that both patients and physicians underestimate the extent of nonadherence when their estimates are compared with more objective measures [4]. The ability of health care providers and caregivers to identify and measure the degree of nonadherence is also limited. The methods that are the simplest—such as asking the patient directly or providing a self-administered questionnaire to the patient—are the least reliable. By contrast, the most accurate methods—observed ingestion or measured blood levels—are intrusive, costly, and not easily scalable [2].

A large proportion of nonadherence, even in severe psychiatric illness, is not willful refusal to take medication. Patients might forget to take medication, which can be exacerbated by illness sequelae, such as disorganization, lack of insight, and/or cognitive dysfunction. In addition, stigma, adverse effects, cost, and lack of perceived efficacy can also play important roles [5].

The distinction between efficacy—the impact of an intervention under ideal conditions—and effectiveness—the impact of an intervention in routine clinical practice—is critical in designing and interpreting clinical trials. Because nonadherence is one of the major drivers of differences in a drug's efficacy vs. effectiveness, the nature of the studies done to assess the impact of medication strategies to enhance adherence becomes a particular challenge.

2. Long-acting injectable antipsychotics

Long-acting injectable medications and implantable formulations were intended to facilitate the benefits of medication by reducing the all-too-likely variability in ingestion. There are now five long-acting injectable (LAI) formulations of antipsychotic medications approved for use in the United States. These medications can be given at intervals of 2−4 weeks depending on their specific pharmacokinetic properties. It is likely that formulations with even longer injection intervals will become available in the not-too-distant future.

In addition to providing ''guaranteed'' medication delivery, LAIs offer other potential advantages. Although when administered LAIs do provide guaranteed medication, they do not provide any overall guarantee that medication will be received, in that a patient may choose to miss a scheduled injection. However, they do provide the advantage of immediate awareness of nonadherence when it does occur, that is, if a patient misses a scheduled injection, the treatment team, family, or other caregiver becomes aware immediately. When individuals are taking oral medication, nonadherence is difficult to detect; the first indication might be a worsening of the patient's condition, which can be too late to prevent further deterioration. In addition, given the pharmacokinetic properties of LAIs, blood levels do not decline as quickly after a missed injection as they would after missing a dose of oral medication. This gives all interested parties time to intervene before an exacerbation is likely. Because LAIs are given parenterally, they also avoid some interindividual differences in absorption and metabolism, which in the case of antipsychotic drugs can lead to enormous and generally unpredictable differences in blood levels [6]. There is also less fluctuation from hour to hour and day to day in the patient's blood level. The use of LAIs can go a long way toward reducing family tension and conflict about medication adherence. Such tensions can be the result of insufficient symptom response secondary to (partial) nonadherence; however, even in adherent patients, tension may be caused by family members' perceived need to check on or remind the patient to take medications.

3. Assessing the comparative effectiveness of long-acting injectable and oral antipsychotics

Despite the availability of a number of LAIs, their utilization rates in the United States are substantially lower than

those in many other countries [7]. A full discussion of the number of potential reasons for this is beyond the scope of this report. However, in the context of the present discussion, it is important to emphasize that the evidence base supporting the use of such agents is both inconsistent and confusing.

Shortly after the introduction of LAIs, a number of mirror-image studies demonstrated their potential in reducing rates of relapse and rehospitalization [8]. Mirror-image studies involve comparing a period before an index event (in this case starting an LAI) with an equal period after the index event. In this analysis, each subject serves as his/her own control. However, although mirror-image studies might suggest effectiveness, they also suffer from the potential impact of other factors besides the introduction of a new treatment, including expectancy bias and changes in service provision and utilization.

The RCT has been the gold standard of comparative effectiveness, and a series of studies have been conducted comparing LAIs with oral medications (either the same specific molecule or an array of other comparable medications given in oral form). In such studies, an immediate challenge is maintaining a double-blind design. One solution is the so-called ''double-dummy'' design in which all patients regardless of assignment receive both injections and oral medications, one of which is a placebo. Other strategies have included using ''masked'' assessors while the type of medication condition is known to the patient. However, concerns have been raised about multiple masked assessors at the same treatment center remaining consistently blind to the treatment type. For this reason and concerns regarding inter-rater reliability, some recent studies have taken advantage of advances in videoconferencing technology and used a small cadre of carefully trained and supervised remote centralized raters who can more easily be kept blind to the treatment condition while maintaining high levels of inter-rater reliability [9,10].

Other considerations in the conduct of RCTs in this context are important, in that they might affect the clinical significance and generalizability of the findings.

First of all, patient selection is a challenge. Should patients be identified for having demonstrated nonadherence leading to a relapse? After all, nonadherence is often covert, undetected, or undocumented when a relapse does occur. How likely are such patients to agree to participate in a controlled clinical trial involving random assignment and a variety of research assessments? Are patients who have a history of or tendency toward nonadherence less likely to participate in RCTs?

One approach to the identification of nonadherent patients is to focus on those who have been hospitalized with a relapse within a specified time from before enrollment in the RCT. The assumption is that because some substantial proportion of these relapses is related to nonadherence, an appropriate sample is being identified. The problem remains that the proportion of such patients included in a particular RCT is unclear, and some populations of recently hospitalized patients might overrepresent those at risk for hospitalization for reasons other than problems in medication adherence, for example, substance use/abuse, lack of social support or housing, environmental stressors, and so forth. The recent study by Rosenheck et al. [9] might be an example of such a population and will be discussed below.

The next concern is the design of the trial in terms of duration, frequency of assessments, monitoring strategies, and other factors that are part of the overall research effort. There has been some suggestion that it is more difficult to demonstrate differences between oral medication and LAIs in short-term as opposed to long-term studies. The rationale is that patients might initially be adherent, that nonadherence might take time to develop, and that the consequences of nonadherence may take several or many months to become apparent. We have previously reported a simulation analysis supporting the possibility that studies lasting 2 years would have substantially more likelihood of detecting a difference than those lasting only 1 year [11].

Another issue in the design of such trials involves the potential effect of the trial itself on patient outcomes (the so-called Hawthorne effect—suggesting that changes in participants' behavior during the course of a study may be related only to the special social situation and social treatment they received [12]). Given the potential for the increased personal attention that is often associated with participation in clinical trials, what role might that play in reducing the risk of nonadherence and/or relapse in a population of patients with schizophrenia? Patients are often sent reminders to attend their appointments for research assessments. In some studies, the medication (either oral or LAI) is provided free to patients and, in the case of the oral drug, even handed to them as one of the incentives for participating in a trial or to have the ''same'' conditions for the LAI and oral medication groups, thereby seriously altering the ecological validity of the study. This provision of oral medications eliminates the need to take a prescription to the pharmacy, which is one point at which patient requirements for initiative might be quite different under normal circumstances. Frequent assessments can be more likely to detect early signs of relapse, allowing the opportunity for clinical intervention to prevent a full-blown relapse in patients receiving oral antipsychotics. This might further diminish the potential advantages of an LAI in clinical trials compared with real-world settings.

4. Results of RCTs

In a meta-analysis published in 2011 [13], we reviewed 10 studies lasting at least 12 months comparing outpatients randomly assigned to LAI or oral medication. Although there were differences in patient characteristics as well as assessment and outcome measures across studies, the

overall analysis suggested significant superiority of LAIs over oral antipsychotics. With 1,700 subjects included in the trials, data on relapse (primary outcome), rehospitalization, nonadherence, dropout because of any cause, inefficacy of treatment, and adverse effects were summarized in a meta-analysis using a random-effects model. Depot formulations significantly reduced relapses, with relative risk (RR) and absolute risk reductions of 30% and 10%, respectively (RR = 0.70, confidence interval [CI] = 0.57−0.87, number needed to treat [NNT] = 10, CI = 6−25, $P = 0.0009$). Furthermore, LAIs also reduced dropout because of inefficacy by 29% (RR = 0.71, CI = 0.57−0.89). Depot antipsychotic drugs also significantly reduced rehospitalization, but because of a number of methodological differences and problems in the individual trials, the evidence was not conclusive.

However, in contrast to these meta-analytic findings, two more recent, large-scale, government-funded studies did not demonstrate the superiority of LAIs over oral medication. One study [9] randomly assigned 369 patients in the Veteran Affairs (VA) system who had been hospitalized within the previous 2 years or who were at imminent risk for hospitalization to either 25 or 50 mg long-acting injectable risperidone or to a psychiatrist's choice of oral antipsychotics. Forty percent of patients were hospitalized at the time of randomization. The rate of (re)hospitalization (the primary outcome measure) was 39% on LAI medication after 10.8 months vs. 45% on oral medication after 11.3 months: hazard ratio, 0.87; 95% CI 0.63−1.20. Although the difference between LAI and oral medication was nonsignificant, the most striking feature of these results is the extremely high rehospitalization rates for both groups. A 39% rehospitalization rate after 10.8 months on depot medication is extremely high, particularly given the contemporary hospitalization usage (studies done 20 or more years ago might reflect a higher likelihood of use of hospital beds). This raises the important consideration that in this particular patient population from the VA system, 37% of whom had active alcohol or substance use, there was high risk of readmission to hospital for reasons other than relapse because of nonadherence. The potential value of LAI treatment depends on reducing the rates of nonadherence; otherwise, there is no evidence that one formulation is more effective in preventing relapse than another.

A second study funded by the National Institute of Mental Health [14] randomized 305 outpatients who had experienced a relapse within the prior year, but not within the past month, to LAI risperidone or an oral second-generation antipsychotic. Patients were followed up for 2 years. Those on LAI had a relapse rate not significantly different from those on oral medication. This population did not have the same characteristics as the study by Rosenheck in terms of chronicity, high prevalence of substance abuse, or high rates of rehospitalization in both treatment groups. However, differences in relapse rates might have been minimized by the nature of the research effort, with, for example, patients being given their oral medication supplies as part of their regularly scheduled visit, and so forth.

Kishimoto [15] presented data from a more recent meta-analysis that included 21 RCTs including the two that were just discussed. This meta-analysis failed to show superiority of LAIs over oral medications ($n = 4{,}950$, RR = 0.93, 95% CI = 0.80−1.08, $P = 0.35$). This meta-analysis is potentially vulnerable to a cohort bias in that significant advantages of LAI medications were more likely to be seen in studies published before 1992 (and involving only first-generation LAIs) than in those published after 2004 (and involving only second-generation LAIs) and a data set limited by no direct comparisons between first- and second-generation LAIs.

Tiihonen et al. [16,17] reported on two large-scale, observational, follow-up studies using a national registry of patients with schizophrenia in Finland. In both these reports, one of which involved patients who had experienced only one prior hospitalization, LAIs were associated with significantly lower rates of hospitalization than were oral medications. If anything, this methodology might be considered to have a conservative bias, in that physicians making a decision to use LAIs for a particular patient are most likely basing that decision on some clinical information, such as prior difficulty with or reluctance to take oral medication, history of poor adherence, and so forth. Given the possibility of selection bias, the finding regarding the superiority of LAIs could be viewed as even more striking. In addition, a naturalistic sample includes all patients receiving treatment in a particular data set and during a particular period and is not restricted to patients who have proven to be eligible for and consented to an often complex and demanding RCT. Therefore, patients involved in a naturalistic data analysis are likely to be more representative of ''real-world'' patients and settings, yielding findings that are likely to be more generalizable.

5. Lessons to be learned for effectiveness research

These diverging results from studies using very different methodologies create an interesting dilemma for comparative effectiveness research and perhaps serve as an example of a situation in which the traditional RCT is less likely to provide valid information than other study designs.

All clinical RCTs have limitations in generalizability; however, when the study has a particular focus on nonadherence and its consequences, it may well be that the RCT by its very nature has too much impact on the primary outcome measure, thereby diminishing the possibility of detecting potentially meaningful differences between alternative treatment approaches.

A possible solution to this challenge would be the implementation of a true ''effectiveness trial'' (a prospective RCT that uses broad inclusion criteria, multiple study

sites, and minimal data requirements mimicking standard clinical practice under real-world conditions of use).

Such a study should be conducted comparing LAIs and oral antipsychotics. Ideally, it should focus on patients in a relatively early phase of illness, before a potential pattern of multiple relapses and severe decrement in psychosocial functioning has already been established. Patients should be followed up for at least 2 years, with the primary outcome measures being relapse and/or hospitalization, which can be verified by relatively objective measures. No other requirements for frequency of visits or standardized assessment should be used. Patients would still have to consent to the randomization, which would potentially exclude a significant proportion of subjects, particularly because one arm of the study involves injections; there would be no getting around this as a methodological problem. Data from such a trial would provide useful additional information on a comparative effectiveness question that remains an enormous public health issue and has proven to be a considerable challenge to study.

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