Research Review Speaker Series™

Is antipsychotic depot treatment an underutilised gold standard in the long-term treatment of schizophrenia?

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Dr Heres' research interests include antipsychotic depot treatment, psychopharmacology, and clinical study design, with a special focus on bias in drug trials. He has been involved as primary investigator, sub-investigator, protocol author or study coordinator in more than 40 phase II, III and IV clinical trials or investigator-initiated trials, most recently for therapeutics under investigation for the treatment of schizophrenia.

This publication is a summary of a presentation by Dr Stephan Heres, Senior Psychiatrist at the Department of Psychiatry and Psychotherapy at the Centre for Disease Management at the Psychiatric Department, Technical University Munich, Germany. He spoke throughout New Zealand in July/August 2012 on the attitudes of psychiatrists and patients towards depot (long-acting injectable) antipsychotic treatment of schizophrenia, the current efficacy evidence for depot antipsychotic use and the current outcomes of the OASE depot clinic in Munich. He acknowledges that the title of his presentation is a little provocative, but believes that the discussion of depot antipsychotic treatment as first-line therapy for schizophrenia is an important one.

The compliance challenge

It would appear that compliance with oral medications is not just an issue in psychiatry, with studies in a variety of therapeutic areas demonstrating low compliance rates. An example of the impact of non-compliance was demonstrated in a review by Wiegratz et al who analysed contraceptive use in Germany.[1] They found that `ideal' use (no missed pills) of oral ovulation inhibitors was associated with 0.3 pregnancies per 100 women per year, while their `typical' use (50% of women missed at least one pill and 25% at least two pills per cycle) was associated with eight pregnancies per 100 women per year. Dr Heres pointed out that remaining compliant with daily oral drug dosing is a challenge for everyone and that depot antipsychotic treatment makes non-compliance more transparent to treating physicians.

Relapse rates under depot treatment

A recent meta-analysis of 10 randomised controlled trials (RCTs) comparing depot antipsychotic treatment with oral antipsychotic treatment revealed 1-year relapse rates with oral treatment of 35% and with depot of 25%.[2] This 10% difference in relapse rate equates to a favourable number needed to treat (NNT) of 10. This means that if 10 patients were treated with a depot antipsychotic rather than an oral antipsychotic, then one patient would be saved from a relapse.

A recent study using naturalistic data of all people in Finland aged 16-65 years who had their first hospitalisation and a diagnosis of schizophrenia between 2000-2007, and who had not collected any antipsychotic medication within the 6 months prior to admission, investigated non-compliance in first-episode patients.[3] Of 2588 patients hospitalised with a first episode of schizophrenia, 58.2% collected a prescription for an antipsychotic within the first 30 days after hospital discharge, whereas 41.8% did not. In this nationwide cohort, only ≈8% of patients received depot injections as their first antipsychotic medication, but those patients had a 64% lower relapse risk compared with those receiving oral antipsychotic treatment.

Attitudes towards depot antipsychotic treatment

Psychiatrists' attitudes

Dr Heres and colleagues recently undertook a study to answer the question: How much more effective (with respect to relapse prevention) do depot antipsychotics have to be compared to oral antipsychotics before they are prescribed?[4] They asked 106 psychiatrists to consider a hypothetical patient with schizophrenia requiring an antipsychotic and asked them to choose which of two formulations (oral or depot injection) of a single antipsychotic agent they would use given the following scenarios regarding annual relapse rates for oral vs depot injection: 35% vs 35%, 35% vs 30%, 35% vs 25%, 35% vs 20%, respectively. The psychiatrists were informed that the two formulations of the agent had identical efficacy and side-effect profiles. Under the scenario of equal annual relapse rates (35% each), the majority of psychiatrists (81%) chose to prescribe the oral formulation of the agent. This percentage decreased to 62% under the 35% vs 30% scenario, to 36% under the 35% vs 25% scenario and to 11% under the 35% vs 20% scenario (see **Figure 1**). The findings showed that a hypothetical 10% improvement in annual relapse rate with depot over oral antipsychotic was necessary to engender a majority switch from oral to depot use. However, in clinical practice we still see the majority of patients being treated with oral antipsychotic formulations despite their being a demonstrated 10% improvement in relapse rate with depot formulations compared with oral formulations.[2]

A clear gap exists between `knowing and doing' with regard to prescribing depot antipsychotics. A recent study in New Zealand by Miles and colleagues looking at psychiatrists' attitudes to, and knowledge about, depot risperidone found that outdated views regarding depot antipsychotics contribute to the gap between actual practice and what is thought to be desirable.[5]

Over the past two decades, the prescribing rate of depot antipsychotics has decreased worldwide. The prescribing of first-generation depot antipsychotics declined when oral second-generation antipsychotics

entered the market in the 1990s. Psychiatrists at the time hoped that the side-effect profile of these new agents would mean a decrease in compliance issues and no need for depot antipsychotics. In the early 2000s, depot second-generation antipsychotics became available. Interestingly, in China since the late 1990s prescribing rates of depot antipsychotics in Beijing and Shanghai have differed significantly despite these regions falling under the same national treatment guidelines and the same reimbursement criteria. Dr Heres explained that the 4-fold difference seen in prescribing rates is simply due to local attitude (in particular hospital attitude) towards the prescribing of these agents.

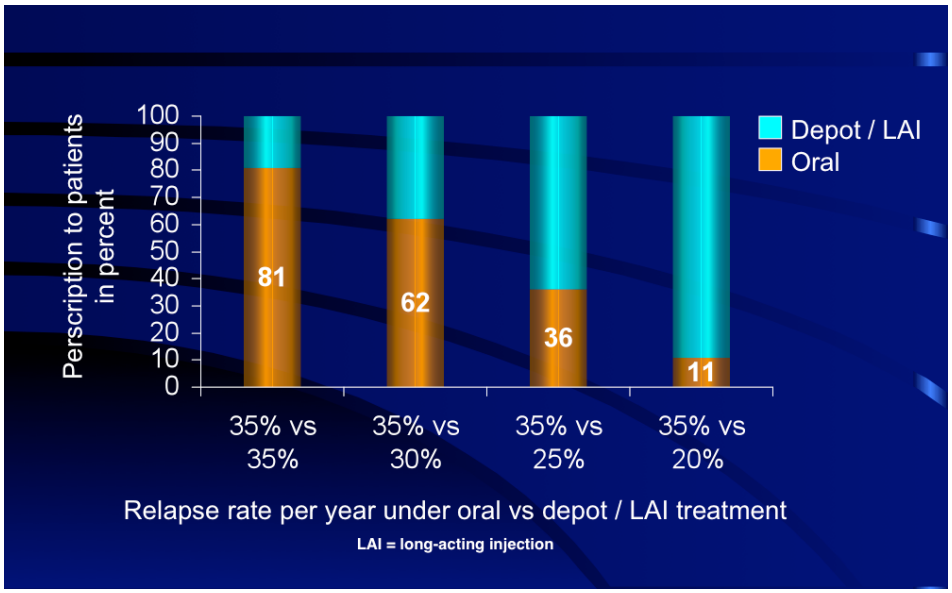

Figure 1. Difference in psychiatrists' choice of antipsychotic formulation when they are presented with hypothetical differences in relapse rates.[4]

Patients' attitudes

Dr Heres and colleagues surveyed 300 patients in nine psychiatric hospitals in Germany about their preference in the mode of administration of antipsychotic treatment.[6] Almost half of the patients were depot antipsychotic-naïve (n = 145), while 60 patients were currently receiving depot formulations, and 95 had previously received such agents. The survey found that overall, >40% of participants would accept depot antipsychotics as a first or second treatment choice. Acceptance rates were 75% in those currently receiving depot antipsychotics, 45% in those with previous depot experience and 23% in depot-naïve participants, indicating that the subjective perception of any benefits from depot treatment rises with depot experience (previous or ongoing). The low rate of acceptance in naïve patients, who are unable to see potential benefits of depot antipsychotic in their particular case, stresses the importance of `peer-to-peer' education aimed at providing patients with first-hand knowledge from patients experienced with such therapy. Interestingly, the rates identified in the survey exceed the current depot prescription rate in Germany of ≈17%. Also of interest, 95% of patients in the survey currently treated with depot antipsychotics had a >3-year history of schizophrenia. This finding lead to the hypothesis that depot treatment was initiated later on in the course of treatment in those patients.

What are the main reasons for not prescribing depot antipsychotics?

Dr Heres and colleagues surveyed 350 German psychiatrists as to their reasons for not prescribing depot antipsychotics (first- or second-generation).[7] They found that most reasons applied equally to first- and second-generation agents, except for direct drug costs (second-generation agents) and risk of extrapyramidal side effects (first-generation agents). The main reason given for not prescribing depot antipsychotics was `good compliance with oral antipsychotic treatment'. Dr Heres pointed out that this attitude is problematic as numerous publications, including the one discussed above regarding oral contraceptive use, have shown that patients struggle daily to remain compliant with oral medications. He stressed that good compliance with oral antipsychotic treatment is not a good reason for not prescribing depot antipsychotics.

The survey also found that only 35.5% of all patients suffering from schizophrenia have ever been offered depot antipsychotic treatment.[7] Furthermore, first-episode schizophrenia patients are rarely considered for depot antipsychotic treatment. This was a robust outcome, with subsequent surveys by Dr Heres and colleagues showing the same findings.

First-episode schizophrenia patients

The question arises as to why psychiatrists are so hesitant to prescribe depot antipsychotics to patients experiencing a first episode of schizophrenia. One explanation may be that in the 1990s first-episode patients were treated with oral second-generation antipsychotics and there was no new evidence available regarding depot use in first-episode patients. In the past few years, increasing evidence has become available regarding the use of depots in such patients.

Results from a 2-year trial in South Africa by Emsley and colleagues investigating the use of depot risperidone 25-50 mg every 2 weeks for 2 years in 50 patients with first-episode schizophrenia revealed that >70% of patients stayed on the study drug until study completion and that <10% of patients experienced a relapse.[8]

Emsley et al subsequently compared their depot risperidone findings with those from a study of 47 first-episode patients randomised to receive either oral risperidone or oral haloperidol.[9] They found a 4-fold higher relapse rate in recipients of oral antipsychotics compared with those who had received depot risperidone. Dr Heres pointed out that one must be careful when extrapolating data such as this from different agents, and that while it might not be fair to say that there is a 4-fold difference in relapse rate, it would be fair to say that the rate of relapse was certainly higher under oral treatment.

Remission, as defined by the Remission in Schizophrenia Working Group, is a favourable outcome associated with a lower relapse rate, better quality of life and a better level of functioning.[10] In Emsley et al's study of depot risperidone, 64% of patients reached remission.[8] Of significance, 97% of those achieving remission on depot risperidone maintained this status until the end of the study compared with only approximately one-third of those receiving oral antipsychotics.[8,9]

At the end of their 2-year depot risperidone trial, Emsley and colleagues asked the 34 remaining responders if they would like to discontinue depot treatment and 33 patients said yes (one patient had been lost to follow-up).[8] It is possible that all of those patients hoped to be in the small group of patients who suffer from only one episode of schizophrenia in their life-time. Follow-up of the 33 patients revealed relapse rates of 79% at 12 months, 94% at 24 months and 97% at 36 months.[11] Symptom severity returned to levels close to those of the first episode and the onset of recurrence symptoms was fairly abrupt. Dr Heres pointed out that most guidelines recommend first-episode patients receive antipsychotics for 1-3 years, but this is based on fairly scant research. Intermittent therapy is not recommended.

White matter changes in first-episode patients on antipsychotics

Individuals with schizophrenia appear to have a dysregulated trajectory of frontal lobe myelination. Bartzokis et al have recently shown that first-episode schizophrenia patients exhibit a shift from white to grey matter in the frontal lobe of the brain.[12] This shift can be halted by treating patients with oral atypical antipsychotics, but after approximately 12 months the shift from white to grey recurs. Bartzokis et al speculated that this phenomenon may be due to medication non-compliance, and so investigated if these changes occur with depot antipsychotics. After 12 months

of treatment with oral risperidone, patients were randomised to either continue oral therapy (n = 13) or to receive depot risperidone (n = 11), and were compared with 14 healthy controls. Inversion recovery MRI at 6 months revealed that white matter volume remained stable in depot risperidone recipients, but decreased significantly in oral risperidone recipients, resulting in a significant differential treatment effect. Furthermore, tests of frontal lobe function revealed that white matter increase was associated with faster reaction times. Reaction times for those receiving depot risperidone did not differ significantly from those of healthy volunteers, while those receiving oral risperidone had significantly slower reaction times.

The OASE project

Dr Heres explained that Oase is the German word for Oasis, but also stands for Optimised Ambulatory outpatient treatment of Schizophrenia. All patients attending the OASE clinic in Munich receive depot antipsychotics and approximately two-thirds are co-treated with oral antidepressants or mood stabilisers. The OASE project was initiated because, as with oral antipsychotics, patients on depot treatment have a tendency to discontinue their treatment over time. The idea was to start patients on depot antipsychotics and use the OASE clinic to keep them on track. To this end, the clinic was designed to appeal to patients with spacious rooms, pleasant décor, free Internet access and free refreshments. Previous surveys have shown that these are the sorts of things that patients desire from such clinics.

At the OASE clinic, patients have access to stable contact persons and there are extra rooms for injection nurses. Dr Heres stressed that in a depot clinic, injection nurses are extremely important and that patients at the OASE clinic have a very good therapeutic alliance with the nurses. He also explained that unlike New Zealand, Germany does not have Compulsory Treatment Orders.

Quarterly assessment of non-compliance risk

As patients have to show up at the depot clinic in order to receive treatment, it is important to identify those at highest risk of not turning up. Furthermore, approximately two-thirds of patients attending the clinic are co-treated with oral agents and identifying patients at risk of becoming non-compliant with those agents is important. To this end, patients involved in the OASE project undergo quarterly routine assessment of non-compliance risk, assessed using a 70-item questionnaire.

Compliance support programme

Several support groups are available to patients attending the OASE clinic and include music therapy, a `nicer-living' group and cultural activities. All patients undergo psychoeducation, receiving booster sessions every 6 months. Patient's families are also strongly encouraged to partake in psychoeducation as this has a very good compliance-enhancing effect. Metacognitive training is utilised, as is motivational interviewing. Each patient is assigned an individual case-manager. A voucher incentive system has also been implemented, where patients earn points for partaking in the compliance support programmes. Points can then be exchanged for vouchers for the purchase of goods at various stores.

First results from the OASE project

Depot risperidone recipients

Depot risperidone became available in Germany in 2003. Eighteen-month completer analysis of mild-to-moderately ill patients (n = 120; mean age 41 years; 61.9% female; 58.2% in remission) in the OASE project receiving depot risperidone for schizophrenia or schizoaffective disorder revealed dropout rates of 34.2% at 12 months and 41.7% at 18 months (unpublished). A study recently undertaken in New Zealand by Carswell and colleagues revealed a depot risperidone discontinuation rate of 42% at 12 months.[13] These findings help highlight the benefit of the OASE project with regard to treatment compliance. Reasons given for dropout from the OASE project were: patient's decision 58%; treating psychiatrist changed 16%; side effects 8%; participation in the programme deemed too elaborate 2%; patient moved 2%; lost to follow-up 2%; no reason stated 12%.

Analysis of the primary end-point, inpatient days, in patients receiving depot risperidone, revealed a 90% decrease in the number of days in hospital after entry into the OASE project; mean 72.1 days in hospital per patient per year and 73.5 days per patient per 18 months prior to entry into the OASE project, compared with 8.1 inpatient days per patient per year and 7.5 inpatient days per patient per 18 months after entry into the project (see **Figure 2**). Quality of life, health status and medication adherence also remained stable in these patients at 12 months. Dr Heres pointed out that a lot of effort has been invested in the OASE project and it is not possible to maintain this for patients long-term. He commented that it maybe more realistic to expect a 40% decrease in the number of inpatient days for patients partaking in such a programme.

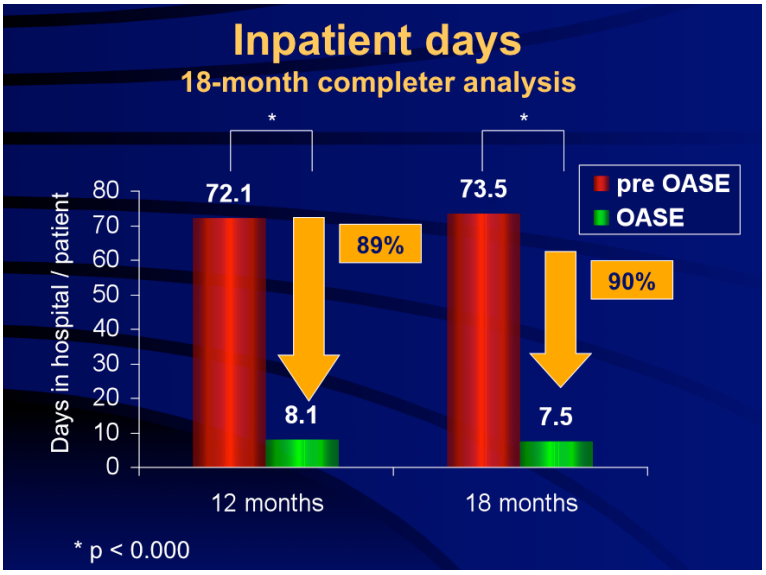

Figure 2: Inpatient days in patients receiving depot risperidone prior to and during participation in the OASE project.

Depot olanzapine recipients

Depot olanzapine has only been used in Germany for approximately 3 years and while the numbers of users is growing each month, there were only 17 patients on the agent included in the 18-month OASE completer analysis. Most of the patients received an oral equivalent olanzapine dose of 15-20 mg/day. At baseline, 70.6% were in remission. The dropout rate was 23.5% at 12 months and 35.3% at 18 months (unpublished findings).

Analysis of inpatient days during the 12 months before and after entry into the OASE project revealed a decrease of 89% (74.5 vs 8.1 days in hospital per patient); eighteen-month values were 103.6 vs 23.8 days per patient, a 77% decrease (see **Figure 3**). The Clinical Global Impression – Severity of Illness Scale score did not differ significantly between baseline and after 12 or 18 months (ranging between 3.2 and 3.5). This finding was consistent with that of McDonnell et al who looked at the long-term safety and efficacy of depot olanzapine for schizophrenia.[14] Quality of life, health status and medication adherence also remained stable among the 17 depot olanzapine recipients at 12 months.

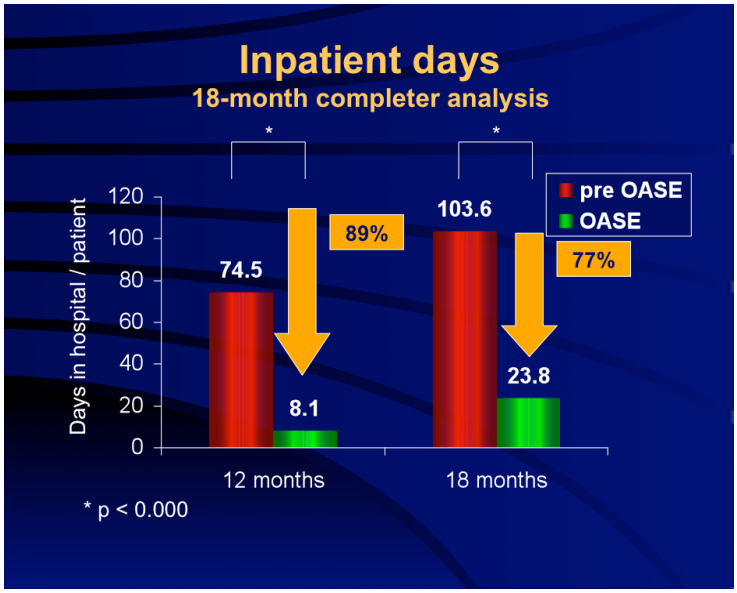

Figure 3: Inpatient days in patients receiving depot olanzapine prior to and during participation in the OASE project.

Engaging patients for antipsychotic depot treatment - experience from the OASE project

Dr Heres outlined the following key ways in which the OASE project has engaged patients with depot antipsychotic treatment:

- All patients with schizophrenia or schizoaffective disorder must be offered depot treatment routinely (100% approach); explicitly including all first-episode patients
- Hand-over of detailed, balanced information on benefits and disadvantages of depot compared to oral drug treatment (manuscript-based). Also, cases of individual patients taking either an oral or depot antipsychotic and how they reached their treatment decision.
- Shared decision-making in order to engender greater compliance
- Peer-to-peer approach (a depot-experienced patient talks about her/his experience with this formulation). This is highly appreciated by patients and is a key intervention for handing over information regarding depot use and how this might be beneficial to an individual patient
- Early introduction of the depot idea during the hospital stay
- Early contact to the OASE team and the OASE facilities

Do we currently exploit the full potential of depot antipsychotics?

Dr Heres concluded his presentation with the following remarks regarding the current status of depot antipsychotic treatment and reminded the audience that drugs only work in patients who take them!

- Depot antipsychotic therapy is still an exceptional approach rather than a routine treatment strategy – despite considerable advantages!
- Psychiatrists anticipate a negative attitude of patients toward depot treatment – such patient attitude is not verified in surveys!
- First-episode patients are rarely treated with depot antipsychotics
  - despite growing excellent evidence for their use!
  - why do we have to wait until the first relapse?
- Depot antipsychotic initiation is a `first step'
  - additional supportive programs help further optimise treatment outcomes and keep patients `in the boat'

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