Research Review Speaker Series™

Long-acting antipsychotic formulations – on their way out or up?

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Professor Taylor has published around 200 research and review papers. His interests include naturalistic outcome studies, pharmacokinetics and pharmacoeconomics. He has also written or edited several books including Schizophrenia in Focus (Pharmaceutical Press), The Use of Drugs in Psychiatry (Gaskell) and Case Studies in Psychopharmacology (Dunitz).

Professor Taylor has been the lead author of the Maudsley Prescribing Guidelines since their inception in 1993. The Maudsley Prescribing Guidelines have sold over 150,000 copies and been translated into seven languages.

This publication is a summary of a presentation by Professor David Taylor, Director of Pharmacy and Pathology at the Maudsley Hospital, South London, Professor of Psychopharmacology at King's College, London and Honorary Professor at the Institute of Psychiatry. He spoke throughout New Zealand in November 2011 about the use of long-acting antipsychotic formulations in the treatment of schizophrenia.

Do antipsychotics work?

Evaluation of UK National Health Service (NHS) psychiatry bed numbers from 1850 to 2007 revealed a sharp decline in the number of beds from 1955 onwards.[1] This decline occurred despite exploding population numbers (from 17 million in 1850 to 61 million in 2007) and coincided with the licencing of the first antipsychotic agent to treat schizophrenia, chlorpromazine, in 1955.[1]

How do we use antipsychotics?

The Maudsley Prescribing Guidelines contain fundamental guidance on how to treat patients with schizophrenia.[2] Firstly, and ideally, the choice of antipsychotic should be agreed upon by the patient and/or carer. The agent, usually a second-generation antipsychotic, should then be titrated to the minimum effective dose, and this dose adjusted according to response and tolerability. The Maudsley Guidelines recommend assessing the patient over 6-8 weeks. Prof. Taylor pointed out that in practice, very few clinicians would persist for that long in the context of no response. In fact, one of the authors of the Maudsley Guidelines has reviewed data on antipsychotic response and is of the opinion that if the patient shows no response at all after 2-3 weeks then one should abandon treatment with that particular antipsychotic as the patient is unlikely to ever show a response to it. If the agent is effective, then it should be continued at the effective dose. If the agent is not effective, then the use of a different second-generation antipsychotic or a first-generation antipsychotic should be considered. If the initial agent is not tolerated this should be discussed with the patient and the agent changed. If compliance is poor, but the agent tolerated, then consider the use of a depot antipsychotic, compliance therapy, or compliance aids.

Acute exacerbations of schizophrenia in a patient taking the drug that they were discharged on, are more difficult to manage. Evidence suggests that if the same drug is maintained at the same dosage the effects will be pretty much the same as increasing the dose of the agent or changing the drug. The Maudsley Guidelines recommend firstly assessing patient adherence to the medication. If the patient is found to have been fully compliant, then initially continue with the usual agent and add supportive measures including acute drug therapy, possibly in the form of a short-term sedative. Ultimately, a switch to a different agent, possibly clozapine may be required.

What is the best antipsychotic?

Prof. Taylor explained that in 1986 when he first started in psychiatry, he was informed that antipsychotics only differed in their adverse effect profile. This was prior to the widespread use of clozapine. In fact, the introduction of clozapine in 1990 changed the view of antipsychotics, with clozapine showing significantly superior efficacy to other drugs, particularly in refractory schizophrenia.

The EUFEST (European First-Episode Schizophrenia Trial) study group compared the efficacy of second-generation antipsychotics with that of a low dose of haloperidol in first-episode schizophrenia in their randomised controlled trial.[3] The main outcome was time to treatment discontinuation. The open-label, pragmatic randomised study showed the following overall rates of treatment discontinuation at 12 months for any cause: olanzapine 33%; amisulpride 40%; ziprasidone 45%; quetiapine 53%; haloperidol 72%.[3]

An open-label inpatient study undertaken by McCue et al in 2006, also comparing the effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia, revealed olanzapine followed by haloperidol and risperidone to be the most effective agents; effective in 92%, 89% and 88% of patients, respectively.[4] In that study, quetiapine, ziprasidone and aripiprazole were all effective in 64% of patients. The efficacy of olanzapine was also demonstrated in the Lilly-funded 3-year observational SOHO (Schizophrenia Outpatients Health Outcomes) study involving 7728 patients.[5] In that study, olanzapine was associated with a lower rate of discontinuation at 36 months, and this rate was almost as low as that seen with clozapine: clozapine 33.79%; olanzapine 36.44%; risperidone 42.66%; depot typical 50.18%; amisulpride 50.35%; oral typical 53.12%; quetiapine 66.05%. The difference in efficacy amongst the antipsychotic agents has been clearly demonstrated in both randomised trials and non-randomised observational studies.

A recent Finnish nationwide cohort study by Tiihonen et al investigating the risk of rehospitalisation after a first hospitalisation for schizophrenia in 2588 patients revealed that the use of depot antipsychotics was associated with a significantly lower risk of rehospitalisation than the use of oral formulations of the same agents (see **Figure 1).**[6]

The observation that not all second-generation antipsychotics are equal in their superiority over first-generation agents was demonstrated in a meta-analysis by Davis et al in 2003.[7] Their analysis, which included 124 randomised controlled trials, revealed that clozapine, amisulpride, risperidone and olanzapine were significantly more efficacious than first-generation antipsychotics, while aripiprazole, quetiapine and ziprasidone were not more efficacious than the first-generation agents.

Leucht et al subsequently showed almost identical findings in their more recent meta-analysis.[8] Their analysis revealed that the four agents, amisulpride, clozapine, olanzapine and risperidone separated from first-generation antipsychotics and showed superior efficacy for overall symptoms and for both positive and negative symptoms (see **Figure 2).** Also apparent in the meta-analysis was that quetiapine was less effective than first-generation antipsychotics for positive symptoms. With regard to depressive symptoms, amisulpride, aripiprazole clozapine, olanzapine and quetiapine were more efficacious than first-generation antipsychotics. All of the second-generation antipsychotic agents investigated in the meta-analysis were associated with fewer extrapyramidal side effects than haloperidol.

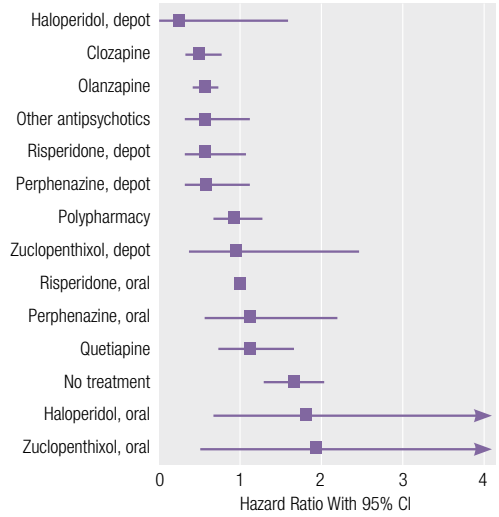
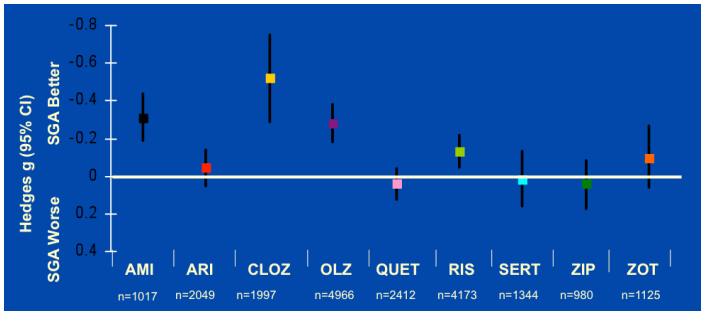


Figure 1: Risk of rehospitalisation after a first hospitalisation for schizophrenia, by antipsychotic treatment.[6]



AMI: amisulpride; ARI: aripiprazole; CLOZ: clozapine; OLZ: olanzapine; QUET: quetiapine; RIS: risperidone; SERT: sertraline; SGA: second-generation antipsychotic; ZIP: ziprasidone; ZOT: zotepine

Figure 2: Findings from a meta-analysis showing that four second-generation drugs, amisulpride, clozapine, olanzapine and risperidone were more efficacious for the treatment of overall schizophrenia symptoms than first-generation drugs.[8]

A comparison of olanzapine and aripiprazole in the treatment of schizophrenia was undertaken by Kane et al who performed a 28-week, randomised, double-blind study looking at the primary endpoint of time to all-cause treatment discontinuation due to poor efficacy.[9] A total of 281 patients received olanzapine 10-20 mg/day and 285 received aripiprazole 10-30 mg/day. The findings revealed that olanzapine out-performed aripiprazole. However, this was not as striking as the difference between olanzapine and quetiapine seen in a study investigating schizophrenia relapse rates at 6 months: olanzapine relapse rate ≈ 20%; quetiapine relapse rate ≈ 80%.[10]

Prof. Taylor pointed out that while there are obvious differences in the efficacy of the agents, it is not entirely clear how this translates into clinical practice. With olanzapine for example, is it that patients get slightly better than they would get on quetiapine, or is it simply that more patients respond to one agent than the other. He suspects that it is the latter scenario and this was ably demonstrated by an observational study of first-episode schizophrenia undertaken in Toronto.[11] The study used a treatment algorithm that moved 244 patients through two antipsychotic trials, followed by a trial with clozapine. Treatment consisted of risperidone followed by olanzapine or vice versa. Of those receiving olanzapine first-up, 82% responded while 66% of those receiving risperidone first-up responded. When those patients were switched to the other agent, 4% responded to risperidone while 26% responded to olanzapine. When patients in both groups were switched to clozapine, an astonishing 75% responded. This is a great advertisement for pertinent use of clozapine as a strictly third-choice agent. Often in clinical practice, we switch from risperidone to olanzapine to one other antipsychotic agent after the next and then finally prescribe clozapine. By that time we have selected out patients who are more refractory to treatment and the response to clozapine is often lower than expected.

Prof. Taylor believes that New Zealand probably leads the world in respect to getting close to the treatment protocol used in the Toronto study and has the highest proportion of clozapine use compared with many other developed countries.

What is the role of depots?

Depot (long-acting) antipsychotics had a poor reputation before the atypicals were made into depot formulations. Over time, depots reduce the risk of relapse and hospitalisation. This was first shown in a study by Hogarty et al who compared long-acting fluphenazine decanoate with oral fluphenazine. Their study revealed that while there was no difference at 12 months in the number of patients relapsing between the two formulations, there was a large difference at 2 years.[12] As mentioned above, Tiihonen and colleagues also demonstrated such a phenomenon with depots in their study analysing rehospitalisation rates.[6] They showed that haloperidol recipients were only 12% as likely to relapse on the depot agent as they were to relapse on the oral formulation of the agent. This represents a huge difference in the risk of relapse.

Conventional depots

Conventional depots (typical depots) have been used for 40 years and are associated with a high rate of extrapyramidal symptoms.[13] The administration of long-acting antipsychotics is complicated by delayed release of the agent and changes in plasma levels without changes in dose.[13] There is a lack of data establishing clear dose requirements with these agents. The original trials of antipsychotic depots were carried out in the 1970s in a fairly haphazard manner. Prescribers in those studies were able to prescribe pretty much whatever dose they felt like. As a consequence, recommended dose ranges vary widely. For example zuclopenthixol decanoate can be prescribed anywhere between 100 and 600 mg/week, which is a 6-fold difference in dose.

Prof. Taylor pointed out that antipsychotics work a bit like paracetamol in that they either work or they do not, and they don't exhibit a gradation response like opiates. He says that we need to establish a small dose range for these agents in order to treat patients optimally. This range may be simply determined by plotting dose against risk of relapse. He has untaken this for haloperidol decanoate, and found the optimal dose for that agent to be ≈100 mg every 4 weeks.[14]

With regard to depot dosing, the efficacy and tolerability of the agent is usually evaluated after 2-3 weeks of treatment and this time point is often much earlier than the attainment of steady state (SS) plasma concentrations. This phenomenon is detailed in **Figure 3.** Each additional dose of the depot adds to the previous dose and it is usually not until four doses of the agent have been administered that SS is achieved. In fact, the plasma concentrations at SS may be 3- to 4-fold higher than after the first dose. Therefore, patients often end up receiving higher doses of the agent than they actually need.

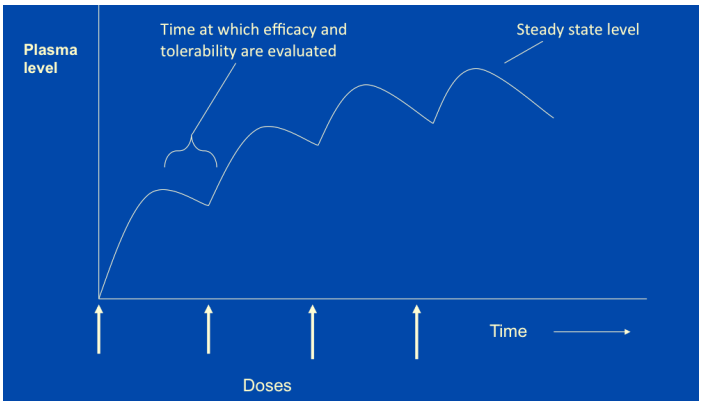


Figure 3: Attainment of steady state with classical depot antipsychotic agents. Steady state is usually not achieved until four doses of the agent have been administered.

Atypical long-acting injections

Risperidone

With the newer atypical agents we have a better understanding of optimal dose ranges. Long-acting risperidone [Risperdal® Consta®], which has been available for nearly 10 years, has a peculiar pharmacokinetic profile where nothing is released for the first 3 weeks.[15,16] Furthermore, the time to SS is 2-3 months, the Cmax is 4-5 weeks and the t1/2 allows for 2-weekly administration. The initial delay in release of the agent can be problematic and the patient may need prolonged hospitalisation and oral antipsychotic supplementation until the agent starts to work. The delayed time to SS can also be a problem, with many clinicians not reassessing the patient at that time point. However, the peak and trough plasma concentrations of long-acting risperidone are less variable than with the oral formulation of the agent.

When Prof. Taylor and colleagues started using Risperdal® Consta® in their unit, they monitored everyone starting the agent and followed them for 3 years. Studies published on the findings of their monitoring detail how 84% of the 211 patients starting Risperdal® Consta® had discontinued the agent at 3 years.[17] Prof. Taylor explained, however, that quite a lot of those patients had in fact switched to the oral formulation of the agent when their condition had improved. Even so, the study did show that 36.2% discontinued Risperdal® Consta® because it was ineffective. Analysis of outpatient or inpatient status revealed that inpatients did worse on Risperdal® Consta® than outpatients and this stands to reason given that inpatients have worse baseline disease. They also found that dose was a very important factor in terms of outcome; a dose of >25 mg every 2 weeks was considerably more effective than a dose <25 mg every 2 weeks for both inpatients and outpatients. Overall, and contrary to

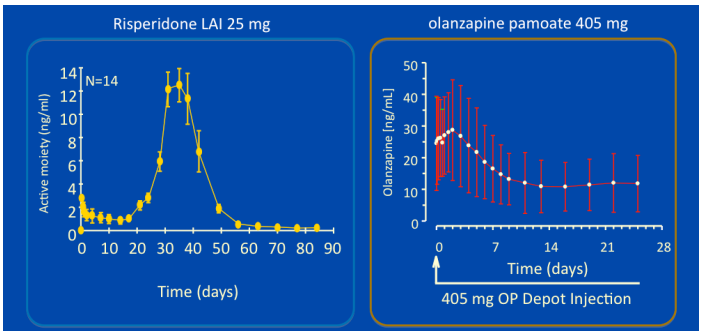
what they expected from the use of a depot, the agent did not appear to be reducing the number of days spent in hospital when compared to the 3 years prior to the initiation of Risperdal® Consta®.[18]

A possible explanation for the observation by Taylor et al is that the 25 mg IM dose of Risperdal® Consta® is too low for many patients. The findings of a Norwegian group of researchers support this concept.[19] They showed that a 25 mg IM dose of long-acting risperidone administered every 2 weeks equates to a risperidone serum concentration lower than is achieved by a 2 mg/day oral dose of risperidone. Given that most patients require a 4-6 mg/day oral dose of the agent in order to achieve a plasma concentration above the threshold of response (20 ng/mL), the 25 mg IM dose is too low, with only a few individuals on this dose achieving the threshold concentration. In fact, the 25 mg IM every two weeks dose only equates to an oral dose of 1.5-1.75 mg/day. Even at a 37.5 mg IM dose, not all patients reach threshold plasma levels.

Other data suggesting that adherence to Risperdal® Consta® is not as good as expected comes from a 12 000 patient US observational study looking at medication adherence. The study revealed that less than half of patients on long-acting risperidone continued treatment with the agent for 18 months.[20]

Olanzapine pamoate [Zyprexa Relprevv®]

Olanzapine pamoate has a favourable pharmacokinetic profile, and is unlike the other atypical long-acting injections on the market. Unlike long-acting risperidone, olanzapine pamoate is released into the blood stream straight after the injection (see **Figure 4**). There is then a slow, continuous release of the agent for some weeks. The early release of olanzapine following the IM injection means that oral antipsychotic supplementation is not required.



LAI: long-acting injection; OP: olanzapine pamoate

Figure 4: Pharmacokinetic profiles of risperidone long-acting injection [Risperdal® Consta®] and olanzapine pamoate [Zyprexa Relprevv®].[15,16]

One of the many studies showing the efficacy and safety of olanzapine long-acting injection was a 24-week, randomised, double-blind trial of maintenance treatment for patients with schizophrenia.[21] The study by Kane and colleagues involved 1065 patients who had been receiving open-label oral olanzapine for 4-8 weeks and were then randomised to double-blind maintenance with either olanzapine pamoate depot 405 mg every 4 weeks (medium dose), 300 mg every 2 weeks (high dose), 150 mg every 2 weeks (low dose), 45 mg every 4 weeks (very low reference dose), or oral olanzapine 10, 15 or 20 mg. The 405 mg every 4 week depot dose is equivalent to a 15 mg/day oral dose, 300 mg every 2 weeks equates to 20 mg/day oral dose, 150 mg every 2 weeks equates to 10 mg/day oral dose and the 45 mg every 4 week dose equates to a 1.5 mg/day oral dose. As expected, with regard to time to relapse of schizophrenia, the high dose of long-acting injectable olanzapine pamoate performed the best and the very low dose the worst. The high, medium and low dose groups showed similar efficacy to each other and to the oral olanzapine group. Prof. Taylor explained that this is an expected finding given that the 24-week time point is too short to see any difference in efficacy between oral and injectable forms of the agent. The study authors concluded that olanzapine long-acting injection was efficacious and had a similar safety profile to oral olanzapine, except for injection-related adverse events.

Post-injection syndrome events. The use of olanzapine pamoate has been associated with post-injection sedation syndrome. This agent is not the only drug to be associated with such a syndrome. In 1959, Hoigne described a pseudoanaphylactic or pseudoallergic syndrome that occurred after IM injection of penicillin-procaine.[22] The symptoms described by Hoigne occurred within an hour of receiving the agent and were characterised by an intense fear of immediate death, visual and auditory hallucinations and acute paranoia. It was thought that the insoluble compound was dissolved and either procaine or penicillin entered the brain in high concentrations, causing the effects.

Post-injection syndrome with olanzapine pamoate consists of disorientation, confusion, delirium, sedation, sleep and occasional coma. As occurs with penicillin-procaine salt, it is thought that direct entry of olanzapine pamoate salt into the bloodstream substantially enhances its rate of dissolution and entry into the brain.[23] If such effects are going to occur, they do so within the first few hours, and therefore monitoring is advised for the first 3 hours after olanzapine pamoate injection. Post-injection syndrome following olanzapine pamoate administration occurs at a rate of 0.07% and Hoigne's syndrome at a rate of 0.08%, thus suggesting that there is a shared mechanism, possibly inadvertent delivery of the agent into the bloodstream upon IM injection.[24] Evidence for this phenomenon comes from the case of a patient participating in a 24-week trial of olanzapine pamoate. He experienced post-injection syndrome following his second dose of the agent. Plasma olanzapine concentrations measured at that time were significantly elevated and much higher than those recorded following his first, third and subsequent injections.[23]

A Norwegian colleague of Prof. Taylor has seen two cases of post-injection syndrome with olanzapine pamoate and has pointed out that there have been no fatalities from this syndrome. His colleague described his patients experiencing an event, as being confused, dropping off to sleep and waking up a few hours later.

Lilly have estimated that in a clinic with 60 patients receiving one injection of olanzapine pamoate every 2 weeks, they would see one post-injection syndrome event per year. The FDA in their approval document for olanzapine pamoate stated that assuming a 0.07% risk of post-injection syndrome at each injection, the risk of the syndrome occurring in a single patient receiving the agent for 20 years is less than 5%.[25]

Prof. Taylor believes that it is not the fear of post-injection syndrome that is limiting the use of olanzapine pamoate, but rather the necessity to monitor the patient for 3 hours after administration of the agent.

Paliperidone palmitate

In the UK, paliperidone palmitate (9-hydroxyrisperidone) long-acting injection is rapidly displacing long-acting risperidone as the treatment of choice. In New Zealand, paliperidone palmitate is unfunded. Paliperidone palmitate is initiated with a loading dose and this allows therapeutic plasma levels to be reached within 3-4 days.[26] Studies investigating the efficacy of paliperidone palmitate have shown therapeutic effects and separation from placebo after 4 days.[27] Like olanzapine pamoate, paliperidone palmitate is suitable for acute and long-term treatment and not surprisingly, has shown significant efficacy over placebo for preventing relapse in patients with schizophrenia.[28]

Another advantage of paliperidone palmitate is that higher oral risperidone equivalent doses can be achieved than with long-acting risperidone (maximum risperidone oral equivalent dose 6 mg/day with paliperidone palmitate versus 4 mg/day with long-acting risperidone).

Why not just use typicals?

Prof. Taylor pointed out that the atypicals depots discussed above are expensive drugs. As health authorities do not have unlimited budgets, maybe we should just use typicals. While there are the recognised difficulties with judging appropriate doses of typical depots, they also have a well-known predilection for causing tardive dyskinesia (TD). When Prof. Taylor first visited a psychiatric hospital in 1986, he was struck by the number (almost 50%) of patients experiencing TD.

The epidemic of TD in that era was enumerated in a meta-analysis by Morgenstern and colleagues who examined 21 studies documenting the prevalence of TD between 1966 and 1985.[29] Their analysis revealed that the prevalence of TD in the 1960s increased rapidly into the 1980s, with almost half the patients in mental health institutions exhibiting the condition.

This phenomenon was due not only to the fact that typicals were being used, but due to the fact patients were receiving high doses of these agents. The advent of atypicals has had a favourable influence on the views about dosing of conventional agents. In the 1980s it was not unusual for an admitted patient to receive haloperidol 40 mg/day, whereas this would not happen in the current era.

The SOHO study which evaluated the proportion of patients who developed TD at some point during 3 years of follow-up while receiving an antipsychotic agent for schizophrenia, showed a higher rate of TD in patients taking depot or oral typicals than those taking atypical agents.[30] The higher rate of TD with depots most likely relates to the higher and sustained plasma levels of these agents.

Some clinicians might say that if the dose is correct and is at the lower end of the scale then TD can be avoided. This was shown not to be true, at least in the case of haloperidol, by a group of researchers from Stellenbosch.[31] They found that even low-dose haloperidol (1.68 mg/day for 12 months) induced an unacceptable rate of TD (12.3%).

What about prolactin?

Hyperprolactinaemia occurs mainly with the typicals, but can also occur with amisulpride and risperidone.[32] Adverse effects of hyperprolactinaemia include an increased risk of breast and other cancers, menstrual and sexual function disturbances. One of the more subtle effects of hyperprolactinaemia is a reduction in bone mineral density and this correlates with an increased risk of hip fracture in older patients. Howard et al. found a significant association between antipsychotic use and hip fracture in patients with schizophrenia.[33]

Do antipsychotics shorten your life?

A large 11-year follow-up study of mortality in patients with schizophrenia in Finland showed that compared with current use of perphenazine, the highest risk of overall mortality was with quetiapine and the lowest risk was with clozapine.[34] The lower risk with clozapine was evident despite its associated metabolic and cardiac risks, and appears to be due to a significantly lower risk of suicide in patients taking the agent. The Finnish study also showed

that the metabolically adverse antipsychotic agents do not show a significant disadvantage with regard to risk of death from ischaemic heart disease.[34] In fact, the risk appeared to non-significantly higher with some of the cleaner agents such as haloperidol and risperidone. Another phenomenon that is difficult to explain is that, generally speaking, the longer patients take antipsychotics the longer they live. This is true for all antipsychotics, even those that are known to cause arrhythmia, obesity, hypercholesterolaemia, hyperlipidaemia and diabetes.[34]

The ZODIAC study compared mortality associated with ziprasidone (an agent known to cause QTc prolongation) and olanzapine over a 1-year period in 18,154 patients with schizophrenia.[35] The study showed no significant differences in the following outcomes between the two agents; non-suicide mortality, all-cause mortality, cardiovascular mortality, mortality due to suicide, sudden death, hospitalisation for arrhythmia, hospitalisation for myocardial infarction and hospitalisation for diabetic ketoacidosis.

The findings of the above studies suggest that what we know about surrogate markers for clinically significant adverse events with particular antipsychotics does not necessarily translate into hard clinical outcomes to an extent that we may notice in a large clinical study.

What should we consider when choosing an antipsychotic?

The following are factors for consideration when deciding which particular antipsychotic agent to choose for a patient:

- Reducing the risk of TD/extrapyramidal symptoms
- Hyperprolactinaemia
- Knowing the right dose
- Rapid attainment of steady-state levels
- Low purchase cost
- Cost-effectiveness (within a National Health Service unit)
- Deltoid administration (this may be preferable to gluteal administration)
- Cold storage requirements
- Absence of post-injection syndrome/need for observation
- State of finances
- Interaction potential
- Efficacy/effectiveness
- Effect on mortality

Characteristics of depots

The particular characteristics of the individual depot agents are outlined in **Table 1**.[13,36] The two optimal antipsychotic agents appear to be olanzapine pamoate and paliperidone palmitate, which have loading dose schedules, giving an immediate effect. The problem with paliperidone palmitate is that it is not funded in New Zealand and that it has a high risk of hyperprolactinaemia. The problem with olanzapine pamoate is the requirement for 3 hours post-injection monitoring.

Table 1: Characteristics of the depot antipsychotics[13,36]

Depot	Well-defined optimal dose?	Time to SS	EPSE/TD potential	Delay in effect/ release	Refrigeration?	PIS?
Flupentixol	No: 40-200 mg/2W	2 months	High	Up to a week	No	?
Fluphenazine	No: 25-100 mg/2W	2 months	High	No	No	?
Haloperidol	Yes: 100 mg/2W	2-3 months	High	Up to a week	No	?
Perphenazine*,**	Yes: 100 mg/2W	2-3 months	Moderate	Up to a week	No	?
Pipotiazine	No: 50-600 mg/month	2 months	Moderate	Unclear	No	?
Zuclopenthixol	No: 100-600 mg/month	2-3 months	High	Up to a week	No	?
Olanzapine	Yes: 150-300 mg/2W	2-3 months (but has loading schedule)	Low	No (with loading)	No	Yes 0.07%
Paliperidone†	Yes: 150 mg, 100 mg, then 50-150 mg/2W	2 months (but has loading schedule)	Low to Moderate	No (with loading)	No	?
Risperidone	No: 25 mg?	2 months	Low to Moderate	3-4 weeks	Yes	?

*Not licenced in the UK; **Not registered in New Zealand; †Not funded in New Zealand
EPSE/TD: extrapyramidal side effects/tardive dyskinesia; PIS: post-injection syndrome; SS: steady state

In summary

Prof. Taylor is of the opinion that depot antipsychotics are the better form of treatment, in that they greatly reduce the risk of relapse compared to their oral equivalents. He believes that, generally speaking, depots are on their way up.

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