Landmark Review

The PALMFlexS trial

Making Education Easy

Publication overview

This publication will present and discuss the findings of the PALMFlexS study of the long-acting injectable antipsychotic paliperidone palmitate in patients with clinically stable but symptomatic (non-acute) schizophrenia who were switched from oral antipsychotic agents. This pragmatic, interventional study was designed to provide a more 'real-life' setting for the study of paliperidone palmitate in comparison to typical clinical trials. To this end the study allowed a broad, more representative selection of patients with schizophrenia to participate, for example by including patients with substance abuse issues, co-morbidities and concomitant use of other medications. The trial mirrored clinical practice by switching patients who were not acutely unwell for reasons including patient choice as well as lack of efficacy, or poor tolerability, and by enabling the treating physician to alter the paliperidone palmitate dose to suit the individual patient's needs at their own discretion. Findings from the 6-month study included a significant degree of further improvement in patient symptomology with paliperidone palmitate, regardless of the reason for switching, in these already clinically stable patients. In addition, and importantly with regard to the potential for good long-term outcomes in this cohort, significant improvement on measures of personal and social functioning and reintegration, subjective wellbeing and treatment satisfaction were observed.

About the Reviewer

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Wayne is a psychiatrist with Waitemata DHB, Clinical Director of Awhina Research and Knowledge, and a Clinical Associate Professor with Auckland University School of Medicine. He has had many roles with the RANZCP including that of President, and has also been involved with NZMA and is currently on that organisation's Board. Wayne has had extensive experience in both the treatment of, and research into schizophrenia. He has conducted sponsored research with, and/or received honoraria for services to Otsuka, Pfizer, Roche, Eli Lilly, Janssen, Amgen, Bristol Myers Squibb and GSK.

Abbreviations used in this review

BMI = body mass index
CGI-S = Clinical Global Impressions – Severity
EPMS = extrapyramidal motor symptoms
ESRS = Extrapyramidal Symptom Rating Scale
LOCF = last observation carried forward
Mini-ICF-APP = Mini-International Classification of Functionality, Disability and Health Rating for Activity and Participation Disorders in Psychological Illness
PANSS = Positive and Negative Syndrome Score
PP = paliperidone palmitate
PSP = Personal and Social Performance

Schreiner A et al. A prospective flexible-dose study of paliperidone palmitate in nonacute but symptomatic patients with schizophrenia previously unsuccessfully treated with oral antipsychotic agents. Clin Ther. 2014;36(10):1372-88.

Free full text PDF available http://www.clinicaltherapeutics.com/article/S0149-2918(14)00552-9/abstract

Background

Schizophrenia is a common mental illness which is estimated to have a lifetime prevalence of around 1% in the general population of New Zealand[1] and may be more prevalent in New Zealand Māori, particularly males[2]. It is characterised by positive symptoms such as delusions and hallucinations, negative symptoms including flatness of affect, disturbances of mood, and disorganisation of speech and behaviour. In addition the disease is commonly associated with a range of cognitive and functional deficits. Schizophrenia follows a relapsing-remitting course which is often associated with progressive decline in functional ability with greater exposure to relapse and untreated symptomatology.[3]

Current recommendations for treatment of patients with schizophrenia in New Zealand include a combination of medication (generally with atypical antipsychotics), psychotherapy and social support.[4] It is now recognised that effective therapy involves more than alleviation of acute symptomatology, and that long-term goals should include achievement of remission and recovery.[5,6] Historically clinical trials in patients with schizophrenia have assessed treatment efficacy based on changes in acute symptomatology utilising measures such as the PANSS. In recent years, particularly with the advent of atypical long-acting injectable antipsychotic therapy (LAT), more studies have explored not only changes in stable, non-acute symptomology, but the effects of therapy on maintenance of remission, prevention of relapse, functional ability and patients' subjective experience of their health and wellness. Designing studies to measure these types of outcomes is important in order understand whether therapies can assist participants to achieve important aspirations such as the maintenance of personal relationships, social reintegration and the achievement of education and employment goals.

The PALMFlexS study provides a range of useful data in this regard. The pragmatic design mimics real-world clinical practice, and the outcome measures include not only standard measures of psychopathology such as the PANSS, but a broad range of measures encompassing domains such as personal and social functioning and reintegration, subjective wellbeing and treatment satisfaction. In addition the results provide insights into the potential benefits of switching to LAT for stable patients with remaining symptomology – a cohort who may not otherwise have been routinely considered for LAT.

Paliperidone palmitate

Paliperidone palmitate (Invega Sustenna®) is a long-acting atypical antipsychotic (benzisoxazole derivative) which is given by intramuscular injection (gluteal or deltoid) on a monthly basis. The therapeutic effects of paliperidone are thought to derive from antagonism at the dopamine (D_2) and serotonin ($5HT_{2A}$) receptors.[7]

In New Zealand paliperidone palmitate (PP) intramuscular injection is indicated for the acute and maintenance treatment of schizophrenia in adults. Available strengths include 25, 50, 75, 100 and 150 mg equivalents. The recommended monthly maintenance dose is 75 mg equivalents but patients may benefit from doses between 25 and 150 mg equivalents.[7] Paliperidone palmitate is listed on both Section B of the Pharmaceutical Schedule and on the Hospital Medicines List, and is reimbursed for patients meeting the Special Authority Criteria listed in Table 1. Approvals and renewals are valid for 12 months.

The efficacy and safety of PP has previously been studied in 5 pivotal trials involving 2,142 patients. These have included 4 short-term randomised, placebo-controlled, double-blind fixed-dose clinical trials (3 x 13 week, 1 x 9 week) in patients with an acute relapse of schizophrenia, and a longer-term study which evaluated symptom control and relapse prevention with maintenance PP.[7]

Table 1. Special Authority criteria for paliperidone palmitate

EITHER: The patient has had an initial Special Authority approval for risperidone depot injection or olanzapine depot injection.
OR, ALL OF THE FOLLOWING: • The patient has schizophrenia or other psychotic disorder; AND • Has tried but failed to comply with treatment using oral atypical antipsychotic agents; AND • Has been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment for 30 days or more in last 12 months.
Renewal Criterial (valid for 12 months) • The initiation of paliperidone depot injection has been associated with fewer days of intensive intervention than was the case during a corresponding period of time prior to the initiation of an atypical antipsychotic depot injection.

STUDY DESIGN

Overview

The PALMFlexS (Paliperidone Palmitate Flexible Dosing in Schizophrenia) study was a large, international, multi-centre, prospective, 6-month, open-label single arm, flexible-dose clinical trial of PP in patients with schizophrenia. PALMFlexS was conducted at 160 sites in 120 countries, predominately in Europe. The pragmatic design of the study was intended to mimic real life settings in order to provide results more directly applicable to usual clinical practice than those obtained from typical clinical trials.

This publication reports on findings from PALMFlexS in patients who switched to PP from oral antipsychotics. At the time of switching the subjects were clinically stable but still experiencing symptoms despite an adequate dosage of oral antipsychotic therapy. Additional findings from PALMFlexS in other patient groups switched to PP have been reported separately. Schreiner A et al.[8] (J Psychopharmacol. 2015 May 21. pii: 0269881115586284. [Epub ahead of print]) published outcomes in a similar group (i.e. stable, not acutely unwell but symptomatic despite adequate therapy) who were treated with risperidone long-acting or conventional depot therapy prior to switching to PP. Findings in patients receiving oral antipsychotic therapy who were acutely unwell at the time of switching to PP have been reported by Hargarter L et al.[9] (Prog Neuropsychopharmacol Biol Psychiatry. 2015;58:1-7).

Study population

Patients eligible for the study were adults aged ≥ 18 years who had a diagnosis of schizophrenia according to DSM-IV criteria, and who were inadequately treated with oral antipsychotic therapy. They were judged clinically stable but still symptomatic (change in CGI-S ≤ 1 during the 4 weeks prior to study entry) despite a stable and adequate therapeutic dose of the same oral antipsychotic.

Participants were deemed to have had unsuccessful therapy with their current oral antipsychotic defined as ≥ 1 of the following criteria:

- Lack of efficacy
  - Baseline PANSS ≥ 70
  - Scores of ≥ 4 in ≥ 2 items from the PANSS positive or negative symptom subscales
  - Scores of ≥ 4 in ≥ 3 items from the PANSS general psychopathology subscale
- Lack of tolerability
  - Clinically significant adverse effects
- Inadequate adherence
- Patient preference

Table 2. Exclusion criteria
Diagnosis resulting from substance use or a general medical condition
Antipsychotic naïve
Clozapine therapy ≤ 3 months prior to study entry
At risk of suicide
Current or prior history of tardive dyskinesia
Current or prior history of neuroleptic malignant syndrome
Pregnancy or breastfeeding
Known allergy, intolerance or hypersensitivity to risperidone, paliperidone or their excipients
IV drug use (other substance use was permitted)

Medication protocols

Potential PALMFlexS participants entered a 7 day screening period prior to study entry during which those without previous exposure to risperidone or paliperidone received a ≥ 2-day oral tolerability test with paliperidone extended-release tablets. PP was initiated according to the dosing schedule in Table 3. The patient's existing oral antipsychotic was then tapered and ceased, within 4 weeks where possible.

Existing psychotropic medications used for purposes other than the treatment of symptoms (e.g. for sedation) could be continued at a stable dose if required. Oral antipsychotic medication (paliperidone modified release tablets where possible) was permitted in the event of worsening symptoms of psychosis between study visits. Other long-acting antipsychotics were not permitted. New prescription of benzodiazepines for rescue medication were permitted, as were anticholinergics (benzotropine mesylate or biperiden) for treatment of EPMS.

Table 3. Paliperidone palmitate dosing schedule*		
Time point	**Dose (mg equivalents)**	**Injection site**
Day 1	150	Deltoid
Day 8 (± 2 days)	100	Alternate deltoid
Monthly (from day 38 ± 7 onward)	50-150	Deltoid or gluteal

* The New Zealand datasheet for paliperidone palmitate recommends the initiation protocol above for treatment naïve patients and those switched from oral medications. The second dose may be given at Day 8 ± 4 days.

Outcome measures

For participants switching to PP for lack of efficacy the primary outcome measure was the proportion of patients with a treatment response (≥ 20% improvement in PANSS total score from baseline to endpoint [LOCF]). Maintenance of efficacy from baseline to endpoint (non-inferiority of PANSS) was the primary outcome measure for all other patients. Secondary outcome measures for efficacy are listed in Table 4. Tolerability and safety outcome measures were extrapyramidal motor symptoms (ESRS), body weight, BMI, and treatment-emergent (new or aggravated) adverse events (TEAEs).

Table 4. Secondary outcome measures	
Measure	Scale
Symptoms of psychosis	PANSS total and change, subscales & Marder factors
Illness severity	Clinical Global Impressions - Severity (CGI-S)
Subjective well-being	Subjective Well-being under Neuroleptics Scale total and subscores
Treatment satisfaction	Treatment Satisfaction for Medication Scale (patients) 7 point categorical scale (physicians)
Personal and social performance	Personal and Social Performance (PSP) total and domain scores
Caregiver burden	Involvement Evaluation Questionnaire
Sleep and daytime drowsiness	11-point categorical scale
Abilities critical to social functioning and reintegration	Mini-International Classification of Functionality, Disability and Health Rating for Activity and Participation Disorders in Psychological Illness (Mini-ICF-APP)

Comment: As a practising clinician the most helpful research into efficacy and tolerability is that which includes the groups of people that we are treating. What is often a problem in translating research studies into clinical practice, especially with tightly designed registration studies, is that the inclusion and especially exclusion criteria mean the study population bears little resemblance to that which presents to us for treatment. This study looks at a common clinical group, namely patients with established schizophrenia who are not doing well on current treatment. Importantly it does not exclude subjects who are using substances. The treatment protocols are easily understandable, are similar to those that would be used in clinical practice and do not introduce activity or limitations that make the treatment environment artificial. It uses a standard initiation of dose, but then allows for flexibility depending on clinician choice.

The study does have the limitations that ensue from an unblinded study as is noted in its introduction. The mirror image type design does however provide some strength in interpreting relevance of change. As a switching study (all subjects are already on antipsychotic treatments) there is an inherent risk that those being switched are artificially selected for recently becoming worse, and improvements simply represent a retreat to the mean. A strength of this study is the inclusion of people who have not tolerated previous treatment and who themselves choose to change as well as those for whom current treatment is unsatisfactory from an efficacy perspective. There is also a requirement for there to be stability in both recent treatment and in efficacy measures. Primary and secondary outcome measures are commonly used tools with the rating methods outlined. Especially important is that the PANSS raters were trained for reliability.

RESULTS

Patient characteristics

A total of 593 participants who received ≥ 1 dose of study medication were included in the intent to treat (ITT) analysis. The study population was comprised of predominantly males (63.1%) and the majority (78.6%) were diagnosed with paranoid schizophrenia. They had a mean age of 38.4 years, had been unwell for a mean of 12.1 years, and most (60.7%), had experienced ≥ 2 hospitalisations. The majority of participants had ≥ 1 co-morbidity, including 22.1% with psychiatric co-morbidities and 9% with substance abuse issues. At baseline subjects had a mean PANSS score of 71.5 and CGI-S of 3.9 indicating mild to moderate severity of symptomology.[10,11] Baseline PANSS total scores were 11.7 points higher (80.3 vs 68.2) in patients switching for efficacy vs other reasons.

Patient preference (43.7%) was the most common reason for entering the trial, followed by inadequate efficacy (24.3%), adherence (23.3%) and tolerability issues (8.8%). Patients were switched from risperidone (n = 206), paliperidone modified release (n = 116), olanzapine (n = 101), aripiprazole (n = 65), quetiapine (n = 39), haloperidol (n = 37), amisulpride (n = 29), quetiapine (n = 26), sertindole (n = 7) and ziprasidone (n = 5).

Almost all patients (93.9%) received the protocol-defined initiation regimen (see Table 3.) at Days 1 and 8. The modal maintenance dose was 101.4 mg equivalents in the total group, 106.3 for those switching for lack of efficacy and 99.8 for those switching for other reasons. Concomitant medications including benzodiazepines and anticholinergics were being prescribed for 64.4% of subjects at baseline.

The study was completed by 74.5% of participants overall, and 72.9 and 75.1% of participants who were switched for lack of efficacy or other reasons respectively. Withdrawal of consent (10.1%) was the most common reason for non-completion, followed by adverse events (6.1%) and lack of efficacy (2.5%).

Comment: The patients in this study are much like those we see in everyday practice. Males predominate, most have paranoid schizophrenia and have had the diagnosis for 12 plus years, although there is a lower rate of substance use than we would typically see in New Zealand. The paper is silent on possible inclusion of people subject to treatment orders.

Primary outcome measures

The primary outcome measure in patients switching to paliperidone for lack of efficacy (≥ 20% improvement in total PANSS) was achieved in 61.5% of participants ($p < 0.0001$ for LOCF endpoint vs baseline). For those switching for other reasons the efficacy of paliperidone was confirmed by an observation of non-inferiority on total PANSS (i.e. maintenance of efficacy) from baseline to LOCF endpoint ($p < 0.0001$). A ≥ 20% improvement in total PANSS was achieved by 64.8% of subjects in this group.

Efficacy analysis – PANSS

Significant improvements in PANSS total score were observed in the total group (-11.7; 95% CI -13.0, -10.5), and in those switched for lack of efficacy (-12.1; -14.6, -9.6) or other reasons (-11.6; -13.1, -10.1) all $p < 0.0001$ for baseline vs LOCF endpoint. The proportion of patients achieving an improvement in total PANSS of ≥ 30% was 51.4% overall and was 39.9 and 55.2 for those switched for lack of efficacy and other reasons respectively. The respective figures for participants who achieved an improvement of ≥ 50% were 30.4, 16.8 and 34.8%

Scores on individual PANSS subscales (positive symptoms, negative symptoms, general psychopathology) were also improved significantly from baseline to LOCF endpoint in all study participants and in those switched for efficacy or other reasons (all $p < 0.0001$). Similarly, improvements in PANSS Marder Factor scores (positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, anxiety/depression) were significant at LOCF endpoint vs baseline in the total group and in those switched for efficacy or other reasons (all $p < 0.0001$).

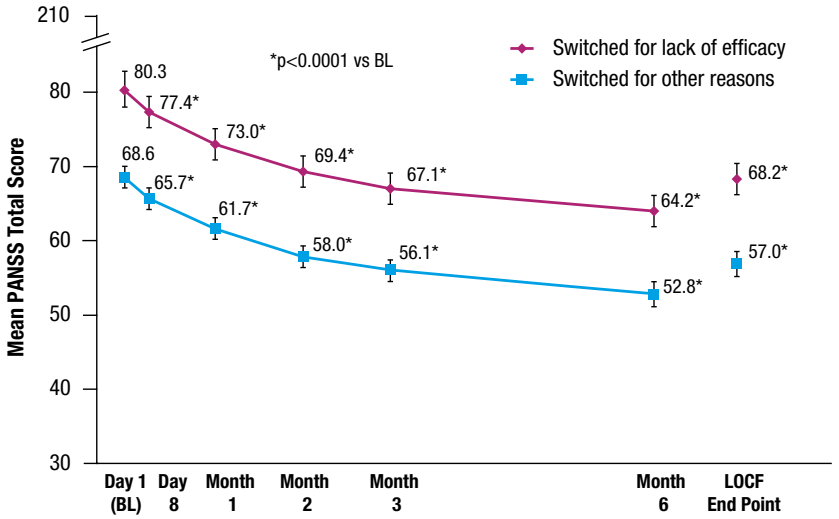

Figure 1. Mean change in PANSS total score over time.
Adapted from Schreiner A et al. 2014

Efficacy analysis – CGI-S

At baseline 31.8% of study participants were rated as having severity of mental illness of mild or less. This improved to 63.2% with PP therapy at LOCF endpoint. The mean CGI-S improved from 3.9 at baseline to 3.3 at LOCF endpoint (-0.6; 95% CI -0.7, -0.5; $p < 0.0001$) in the total group, with similar levels of improvement seen in patients switched for lack of efficacy and those switched for other reasons.

Comment: The efficacy outcome measures show a robust and sustainable change that is at a level that would be likely to be associated with a discernible improvement in state. It is notable that those who switched for reasons other than efficacy also showed reductions in PANSS-assessed symptomatology. The paper describes not only total PANSS changes but also gives changes in the scales, i.e. positive, negative and general, and in the supplement, the Marder Factor scores. This is encouraging as in the past we have seen studies which quote a significant shift but when you examine the subscale data you find it is in irrelevant dimensions.

Efficacy analysis - personal and social functioning

The Personal and Social Performance Scale (PSP) is a 100 point scale which measures personal and social functioning across 4 functional domains; domain A, socially useful activities including work and study; domain B, personal and social relationships; domain C, self-care; domain D, disturbing and aggressive behaviours. Domains A and B are particularly relevant for patients with stable disease, whilst domains C and D tend to be of more importance for patients in an acute phase of the illness. Patients are rated on a 6-point scale by the severity of their functional deficits (absent, mild, manifest, marked, severe, very severe) for each domain. Clinically relevant changes in function are indicated by differences in PSP score of ≥ 8 points.[6]

On entry to the PALMflexS study mean PSP total values were 58.1 (SD 13.4) indicating marked difficulties in 1 of domains A to C, or manifest difficulties in domain D, with the majority of patients (80.6%) in the range 31-70 indicting varying levels of disability. Treatment with PP was associated with a statistically ($p < 0.001$) and clinically (change ≥ 8 points) significant improvement in mean overall functioning to 66.1 (15.7) at endpoint (LOCF). At this level patients would experience manifest, but not marked, difficulties in 1 or more of domains A to C, or mild difficulties in domain D. Patients switched for efficacy had smaller respective improvements in total PSP; 5.5 (12.3) vs 8.8 (14.4) respectively, $p < 0.05$.

The proportion of patients with severe disability requiring intensive supervision or support remained at around 4% throughout the study. However the proportion with only mild functional impairment increased with PP therapy from 15.3% at baseline to 40.8% at endpoint (LOCF).

On the PSP domain A (socially useful activities), 43.9% of participants were rated as having marked to very severe function requiring intensive supervision at baseline. At endpoint (LOCF) this proportion had decreased to 25%. Similarly on domain B (personal and social relationships) the proportion with marked to very severe difficulty had improved from 30.9 to 17.8% between baseline and endpoint (LOCF). On self-care (domain C) the proportion of patients in this most functionally disabled category had decreased from 10.0 to 5.6; for domain D (disturbing and aggressive behaviour) the respective figures were 3.0 and 2.6.

Efficacy analysis - Mini-ICF-APP

The Mini-ICF-APP is a compact scale based on the WHO International Classification of Functioning, Disability and Health (2001) which was designed to assess limitations in capacity (i.e. the ability to conduct activities) in patients with mental illness. It enables assessment of the patient's ability to fulfil roles and functions in 13 areas; mobility; self-care; non-work activities; intimate relationships; group integration; contact with others; assertiveness; endurance; competence to judge and decide; flexibility; planning and structuring of tasks; adherence to regulations. For each domain the patient's ability is rated on a 5-point Likert scale from 0 to 4 (no impairment,

mild impairment, moderate disability, severe disability, total disability) resulting in a total score ranging from 0 to 52.[6,12] In the present study total Mini-ICF-APP scores decreased significantly from baseline to LOCF endpoint (19.8 vs 15.9; $p < 0.0001$) indicating a reduction in illness-related disability. Significant reductions in all 13 Mini-ICF-APP domains were also observed (all $p < 0.0001$).

Efficacy analysis – other measures

Both patients and clinicians rated satisfaction with PP treatment as significantly greater at LOCF endpoint compared to baseline. Subjective Wellbeing under Neuroleptics Scale (SWN-S) scores improved from 80.1 to 85.5 (mean change 5.4; 95% CI 4.0, 6.7) and Treatment Satisfaction Questionnaire for Medication (TSQM) scores improved from 55.9 to 65.0 (9.1; 6.6, 11.7), both $p < 0.0001$. Physicians' satisfaction scores (efficacy, safety, mode of administration, overall satisfaction) were also significantly increased (all $p < 0.0001$). In addition patient drowsiness declined significantly (drowsiness score), and quality of sleep improved (quality of sleep score), both $p < 0.0001$ for baseline vs LOCF endpoint.

Comment: Psychiatrists are often criticised for being only interested in reducing symptoms. It is therefore important this study looks at and reports factors other than symptomatic outcomes. People with schizophrenia ask what good is it in having fewer voices if I feel awful, can't think any better and cannot participate. The measures used in the study for personal and social function are valid ones that are reliably used. The size of the change is likely to be linked to improved personal wellbeing. The study has also monitored the subjective experience of the treatment (crucial since these people will need to be on medication long term) and found improvements from the previous treatments. It confirms findings from other studies that people who are properly initiated on LAT and who experience improvements with it are likely to want to continue.

Safety and tolerability analysis

TEAEs were reported in 59.7% of study participants. Most (93.1%) were categorised as being of mild-moderate severity, and most (75.8%) did not result in a change to PP dosage. TEAEs which occurred in ≥ 5% of study participants are detailed in Figure 2. TEAEs resulting in study discontinuation occurred in 7.1% of subjects.

The rate of EPMS in the study population was low at study entry and declined significantly to LOCF endpoint; mean ESRS 2.8 vs 1.6 respectively, $p < 0.0001$. Similarly rates of anticholinergic usage declined during the study. The proportion of patients who had bodyweight gain of ≥ 7% was 15.4%; mean bodyweight gain was 1.2 kg and mean increase in BMI was 0.4. Adverse events potentially related to hyperprolactinaemia were reported in 3% of subjects. Rates of substance abuse decreased from 9.0 to 6.9% during the trial.

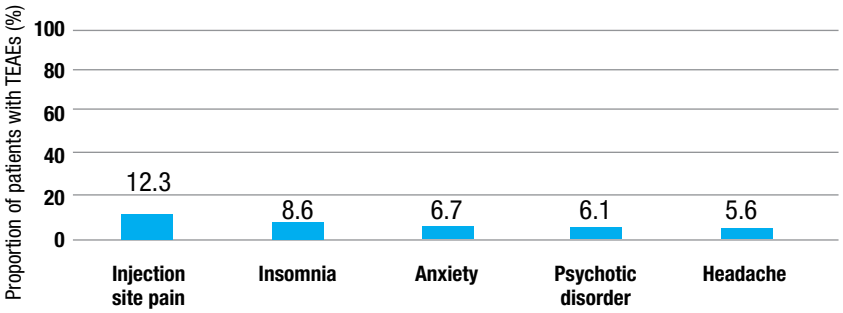

Figure 2. Treatment-emergent adverse events (%) reported in ≥ 5% of study participants (ITT analysis)

CONCLUSIONS

The authors concluded that in stable, non-acute patients with schizophrenia and residual symptomatology, switching from oral antipsychotics to paliperidone palmitate results in "*clinically relevant symptom improvement and improvements in measures of functioning*'.

Comment: There have been a number of papers that address the patterns of use of injectable antipsychotic agents and suggest that they are under-utilised, at least in part, due to physician resistance.[13] Studies like PALMFlexS that are conducted in clinical settings using treatment modalities that are standard and that treat the people who we see will hopefully go some way to diminishing the reluctance to consider this treatment option. It is intriguing that the greatest number of switch subjects were "patient choice". This raises an important question in use of LATs; how often are we, as the treating doctor, introducing the possibility of such treatment? Do we really make it a choice that a patient and their family might make because they see it as a better alternative?

Take-home messages

- **Treatment with PP was associated with statistically and clinically significant improvements in symptomology in this clinically stable group of patients, regardless of the reason for switching:**
  - PANSS improvements ≥ 20, 30 and 50% occurred in 64.0, 51.4 & 30.4% of participants respectively.
  - CGI-S of mild or less increased from 31.8% at baseline to 63.2% at LOCF endpoint.
- **Participants were observed to have significantly improvements in a wide range of functional domains:**
  - PSP mild functional impairment improved from 15.3% at baseline to 40.8% at LOCF endpoint.
  - Significant decreases in Mini-ICF-APP scores indicated a reduction in illness-related disability.
  - Patient satisfaction with treatment and subjective well-being were significantly improved.
- **PP was well tolerated with low rates of adverse events. Of note EPMS severity declined significantly over the course of the study.**

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