PO vs. LAI Antipsychotic Medications
Evidence Based Guide to Policy Making

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Acronyms and Definitions

FGA – first generation antipsychotics. A class of medications also known as typical antipsychotics. It is characterized by exhibiting its antipsychotic action through selectively inhibiting D2 receptor.
Acronyms and Definitions

SGA – second generation antipsychotics. A class of medications also known as atypical or novel antipsychotics. It is characterized by exhibiting its antipsychotic action through various mechanisms of action in addition to or instead of inhibiting D2 receptor.

Examples of such mechanisms of action include:
• 5-HT-2A antagonism
• D2 partial agonism
• 5-HT-1A partial agonism
Acronyms and Definitions

LAI(s) – long-acting injectable antipsychotic(s). A group of medications characterized by their ability to maintain therapeutic plasma level of antipsychotic through injections administered weeks to months apart.

OAP – oral antipsychotic

PO – per os (Latin) is a phrase used in medical practice meaning taking medications by mouth.
Acronyms and Definitions

APA – American Psychiatric Association

RCT – randomized control trial

NNT – number needed to treat
Challenges in Gathering Evidence

Are we comparing apples to apples?

• So few LAIs, so many PO antipsychotics
• In vitro = in vivo?
• Measuring the same outcomes?
STATEMENT 10: Long-Acting Injectable Antipsychotic Medications

APA *suggests* that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.

Presumably due to improved adherence, advantages of LAI antipsychotics include the potential for a decreased risk of mortality; reduced risk of hospitalization; and decreased rates of treatment discontinuation, including discontinuation due to inefficacy.

Other benefits for patients include a subjective sense of better symptom control, greater convenience as a result of needing to take fewer medications daily, and reduced conflict with family members or other persons of support related to medication-related reminders.
STATEMENT 10: Long-Acting Injectable Antipsychotic Medications (Cont.)

In addition, discomfort can often be minimized by using SGA LAIs rather than FGA LAIs, which have sesame oil–based vehicles, or by using an LAI with a small injection volume or lower administration frequency.

[If] an individual has not responded to treatment with an oral antipsychotic medication, a trial of an LAI may be warranted because breaks in the continuity of oral medication therapy can be unrecognized.

Earlier discussion of an LAI may also be considered in individuals who are at increased risk of poor adherence due to a limited awareness of needing treatment or a co-occurring substance use disorder.
PO vs. LAI Summary

• Both options are FDA approved for treatment of acute episodes of schizophrenia and maintenance treatment of schizophrenia.

• Adherence to PO antipsychotics cannot be reliably assessed by patient self-report or by physician estimate.
PO vs. LAI Summary

Patients treated with LAIs when compared to those treated with PO antipsychotics demonstrated lower risks of:

• Treatment failure
• Rehospitalizations
• Drug discontinuation
• Gaps in therapeutic plasma concentrations
• Violence (including in forensic settings)
• Death
PO vs. LAI Summary

Patients treated with LAIs when transitioned from PO antipsychotics had:

• Fewer hospitalization
• Fewer inpatient days
• Fewer ER visits
• Decreased hospitalization cost
• Decreased all medical cost
• Decreased total health care cost
PO vs. LAI Summary

• LAI demonstrated non-inferiority compared to PO formulation of aripiprazole in decreasing the rates of impending relapse.

• Compared to clinician’s choice of care, the use of LAIs for individuals with early-phase schizophrenia produced significant reduction in the incidence rate of first hospitalization.

• Meta-analysis showed no apparent benefit of depot over oral formulations in RCTs.

• There was a significant advantage for depot formulations in prospective and retrospective observational studies.
PO vs. LAI Summary

Compared to patients treated with OAP, patients treated with SGA-LAI are less likely to need antipsychotic polypharmacy, while patients treated with FGA-LAI are more likely to require multiple antipsychotics.

Compared to patients treated with OAP, SGA-LAI patients have higher odds of adherence at 12 months, in contrast to FGA-LAI patients who have lower odds of adherence relative to OAP patients.

SGA-LAI patients were more likely to have no gaps in treatment than OAP patients, but not FGA-LAI patients.
Continuity of care after inpatient discharge of patients with schizophrenia in the Medicaid program: a retrospective longitudinal cohort analysis.\textsuperscript{[2]}

Of the 59,567 hospital discharges (49,239 unique patients), 41.7\% received schizophrenia-related outpatient visits within the first week of hospital discharge. By 30 days, this percentage had increased to 59.3\%.

This means that more than 40\% of patients did not receive follow-up care within 30 days of discharge.
Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia.[3]

Methods

Adult outpatients with schizophrenia (N=35) or schizoaffective disorder (N=26) received adherence assessments via electronically monitored medication vial caps as well as by monthly prescriber, patient, and research assistant report for up to six months.
Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia.[3]

Results

Electronic monitoring detected greater nonadherence rates (57%) than either prescribers (7%) or patients (5%), though the research assistant ratings were 54%. No directional bias was found between electronic monitoring and assignment of adherence by research assistants, although disagreement occurred in 36% of cases.
Examining levels of antipsychotic adherence to better understand nonadherence.\textsuperscript{[4]}

Medication Event Monitoring System (MEMS) cap study found that only 48% of schizophrenia patients took 80% of their doses over 4 weeks, with 17.3% of patients taking \(\leq 20\%\) of their antipsychotic.
Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia.\textsuperscript{[5]}

Method:

Between January 2012 and April 2017, antipsychotic plasma levels were measured in 99 individuals provisionally diagnosed with treatment-resistant schizophrenia by their treating clinicians, but not prescribed clozapine.

Results:

Thirty-five per cent of plasma levels were subtherapeutic, and of these, 34% were undetectable.
Adherence and Long-Acting Injectable Antipsychotics in Schizophrenia: An Update.\(^6\)

Two large observational studies from Finland showed that LAI, as compared to oral formulations of the same drugs, were associated with a significantly lower risk of rehospitalization and drug discontinuation.
Objective:
The study compared the effects of once-monthly paliperidone palmitate with daily oral antipsychotics on treatment failure in adults with schizophrenia.

Method:
Subjects were randomly assigned to once-monthly paliperidone palmitate injections or daily oral antipsychotics (randomly assigned from 7 acceptable, prespecified oral antipsychotics) for 15 months.

The primary end point was time to first treatment failure, defined as arrest/incarceration; psychiatric hospitalization; suicide; treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability; or increased psychiatric services to prevent hospitalization.
PO vs. LAI Literature review


Results
90 subjects (39.8%) in the paliperidone palmitate group and 117 subjects (53.7%) in the oral antipsychotic group had a treatment failure event. Paliperidone palmitate was superior to oral antipsychotics in delaying time to first treatment failure (HR, 1.43; 95% CI, 1.09-1.88; \( P = .011 \)).

Median times to first treatment failure were 416 and 226 days in the paliperidone palmitate and oral antipsychotic groups, respectively.
PO vs. LAI  Literature review


SECONDARY OUTCOMES

*Time to first psychiatric hospitalization or arrest/incarceration.* Seventy-six subjects (33.6%) in the paliperidone palmitate group and 98 subjects (45.0%) in the oral antipsychotic group had a psychiatric hospitalization or arrest/incarceration as a first treatment failure event. Paliperidone palmitate was superior to oral antipsychotics in delaying time to first psychiatric hospitalization or arrest/incarceration (HR, 1.43; 95% CI, 1.06-1.93; \(P = .019\)).

Median time to first psychiatric hospitalization or arrest/incarceration was not reached in the paliperidone palmitate group (> 450 days) and was 274 days in the oral antipsychotic group.
Real-world effectiveness of long-acting antipsychotic treatments in a nationwide cohort of 3957 patients with schizophrenia, schizoaffective disorder and other diagnoses in Quebec. [8]

Higher medication costs were offset by lower inpatient and outpatient costs. Compared to the year before, schizophrenia patients treated with LAIs had:

- Fewer hospitalization (0.9 compared to 2.0)
- Fewer inpatient days (17.3 compared to 52.4)
- Fewer ER visits (3.1 compared to 5.0)
- Decreased hospitalization cost ($17,786 vs. $53,482)
- Decreased all medical cost ($19,721 vs. $55,900)
- Decreased total health care cost ($24,313 vs. $57,790)
Long-acting injectable antipsychotics for prevention and management of violent behaviour in psychotic patients. [9]

• LAI significantly reduced the severity of hostility, aggressivity, number of violent incidents, and criminal offences.

• Available data encourage the use of LAI in forensic psychiatry, especially during court-ordered commitment treatment.
PO vs. LAI  Literature review

Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. [10]

Prospectively gathered nationwide register-based data during 2006–2013 was linked to study all-cause mortality among all patients aged 16–64 years with schizophrenia in Sweden.

Among patients with schizophrenia, LAI use is associated with an approximately 30% lower risk of death compared with oral agents. SG LAIs and oral aripiprazole are associated with the lowest mortality.
Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. [10]

The adjusted risk of death was 56% lower during use of any antipsychotic compared with no use of antipsychotic.

Cumulative mortality rates during maximum follow-up of 7.5 years were 7.5% during SG LAI use, 8.5% during SG oral, 12.2% during FG oral, 12.3% during FG LAI, and 15.2% during no use of antipsychotics.
Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. \[10\]

Concerning specific agents, the lowest mortality was observed for once-monthly paliperidone oral aripiprazole, and risperidone LAI.
Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. [10]

In pairwise comparison, LAIs were associated with 33% lower mortality than equivalent orals.
Hospital Readmission Rates Among Patients With Schizophrenia Treated With Long-Acting Injectables or Oral Antipsychotics. [11]

- LAIs were associated with significantly lower probability of rehospitalization compared with oral antipsychotics at 60 days for schizophrenia-only patients and for all patients.

- The absolute difference in probability of rehospitalization for all patients was significantly lower by 5.0% at 60 days in the LAI group compared with the oral antipsychotics group.

- Compared with use of oral antipsychotics, use of LAIs was associated with fewer readmissions of Medicaid patients with schizophrenia within 60 days after an index hospitalization.
PO vs. LAI Literature review

Do Long-Acting Injectable Antipsychotics Prevent or Delay Hospital Readmission? [12]

Those who received a LAI had a significantly longer survival time (mean 278.0 days) without readmission compared to those who did not (mean 243.6 days).

There was no statistically significant difference in the frequency of one-year readmission between those who did receive a LAI (43.1%) and those who did not (56.9%).

Those who received a LAI with administration frequency of a month or longer had a significantly longer survival time without readmission (mean 307.9 days) when compared to those with a shorter administration frequency (mean 245.0 days).
Early initiation of long-acting injectable antipsychotic treatment is associated with lower hospitalization rates and healthcare costs in patients with schizophrenia: real-world evidence from US claims data [13]

All-cause hospitalization rates were 22.2% in early initiators and 26.9% in late initiators. Of early initiators, 14.1% had a psychiatric hospitalization vs 19.2% of late initiators. Adjusted psychiatric healthcare costs were significantly lower in early initiators compared with late initiators $21,545 vs $24,132.
PO vs. LAI Literature review

Use of Long-Acting Injectable Antipsychotic in an Inpatient Unit of a Community Teaching Hospital. [14]

70% of the patients discharged from the inpatient unit during the study period had Schizophrenia Spectrum Disorders and were eligible for a LAI.

Less than half of the eligible patients (44%) were prescribed a LAI, most of whom were male (84%).

An association between age group (patients aged 41 years or younger) and LAI use was observed ($p < 0.05$), while gender, employment status, living arrangement, length of hospital stay, recent hospitalization, and cooccurring substance use disorder were not.
PO vs. LAI Literature review

Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis.\textsuperscript{[15]}

Objective:
To compare hospitalization rates in patients with schizophrenia treated prospectively with aripiprazole once monthly 400 mg (AOM 400; an extended-release injectable suspension) vs the same patients' retrospective rates with their prior oral anti-psychotic therapy.

End-points:
The primary end-point was the total psychiatric hospitalization rate, defined as the proportion of patients with 1 psychiatric hospitalization.

Secondary efficacy end-points included the 6-month hospitalization rate during prospective aripiprazole once monthly therapy (months 1–6) compared with the 6-month retrospective period (months −7 to −1)
Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis.\(^{[15]}\)

Results:
Psychiatric hospitalization rates were significantly lower when patients were treated with AOM 400 compared with oral anti-psychotic therapy both in the 3-month primary efficacy sample (2.7% vs 27.1) and in the total sample (6-month prospective rate: 8.8% vs 6-month retrospective rate: 38.1).
Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study.\cite{16}

Primary outcome

The primary outcome was the Kaplan–Meier estimated impending relapse rate from the date of randomisation to the end of week 26.

Conclusions

Aripiprazole once-monthly 400mg was non-inferior to oral aripiprazole, and the reduction in Kaplan–Meier estimated impending relapse rate at week 26 was statistically significant v. aripiprazole once-monthly 50 mg.
PO vs. LAI Literature review

Effect of Long-Acting Injectable Antipsychotics vs Usual Care on Time to First Hospitalization in Early-Phase Schizophrenia. [17]

Conclusions

The use of LAIs for individuals with early-phase schizophrenia produced a significant and clinically meaningful 44% reduction in the incidence rate of first hospitalization and an NNT of 7 for the prevention of hospitalization.

Figure 2. Time Remaining Without Having a First Hospitalization
PO vs. LAI  Literature review

Efficacy and Effectiveness of Depot Versus Oral Antipsychotics in Schizophrenia: Synthesizing Results Across Different Research Designs. [18]

Method

A PubMed literature review targeted English-language studies (2000-2011) with information on relapse, hospitalization, or all-cause discontinuation for depot and oral antipsychotic treatment arms in schizophrenia.

13 relevant studies included 5 Randomized Control Trials (RTCs), 4 prospective observational studies, and 4 retrospective observational studies.

Age- and gender-adjusted risk ratios (RRs) (depot/oral) were calculated for the identified endpoints (hospitalization, relapse, discontinuation).
PO vs. LAI Literature review

Efficacy and Effectiveness of Depot Versus Oral Antipsychotics in Schizophrenia: Synthesizing Results Across Different Research Designs. [18]

Figure 2. Meta-Analysis of Adjusted Risk Ratios, by Study Design

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors Depot</th>
<th>Favors Oral</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
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<td>RCTs</td>
<td></td>
<td></td>
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<tr>
<td>Gaebel et al, 2010</td>
<td>0.58</td>
<td>0.39–0.86</td>
<td>0.50</td>
<td>0.38–0.67</td>
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<tr>
<td>Kane et al, 2010</td>
<td>0.58</td>
<td>0.39–0.86</td>
<td>0.50</td>
<td>0.38–0.67</td>
<td>17.14</td>
</tr>
<tr>
<td>Keks et al, 2007</td>
<td>2.03</td>
<td>1.31–3.16</td>
<td>2.03</td>
<td>1.31–3.16</td>
<td>14.38</td>
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<tr>
<td>Macfadden et al, 2010</td>
<td>0.92</td>
<td>0.72–1.18</td>
<td>0.92</td>
<td>0.72–1.18</td>
<td>17.77</td>
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<tr>
<td>Rosenheck et al, 2011</td>
<td>1.07</td>
<td>0.84–1.37</td>
<td>1.07</td>
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<td>17.76</td>
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<td>Pooled RCTs</td>
<td>0.89</td>
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</tbody>
</table>

Abbreviations: RCT = randomized controlled trial, RR = risk ratio.
PO vs. LAI Literature review

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PO vs. LAI Literature review

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Possible explanation for the difference in findings:

RTCs
(+) randomization is the best strategy to estimate treatment effects from a statistical perspective
(-) do not fully reflect other aspects of how oral therapies are used in general clinical practice

Observational studies
(+ ) more realistic treatment settings
(-) possible lack of control for other possible confounding factors and selection bias.
Treatment patterns in Medicaid patients with schizophrenia initiated on a first- or second-generation long-acting injectable versus oral antipsychotic.\textsuperscript{[19]}

Method

Adults with schizophrenia initiated on FGA-LAI, SGA-LAI, or OAP on or after January 2010 were identified using a six-state Medicaid database (January 2009 - March 2015). Outcomes were assessed during the 12 months following treatment initiation.

Index medication adherence was assessed using the proportion of days covered \( \geq 80\% \), while persistence was assessed as no gap of \( \geq 30 \), \( \geq 60 \), or \( \geq 90 \) days between days of supply.

Outcomes were compared between FGA/SGA-LAI and OAP cohorts.
Treatment patterns in Medicaid patients with schizophrenia initiated on a first- or second-generation long-acting injectable versus oral antipsychotic.\textsuperscript{[19]}

Results

During follow-up, AP polypharmacy was more common in FGA-LAI patients (36%) and less common in SGA-LAI patients (27%;) versus OAP patients (33%).

SGA-LAI patients had 24% higher odds of adherence at 12 months, in contrast to FGA-LAI patients who had 48% lower odds of adherence relative to OAP patients.

SGA-LAI patients were more likely to be persistent (no gap ≥ 60 days) at 12 months than OAP patients (37% vs 30%), but not FGA-LAI patients (31% vs 30%).

In comparison to OAP patients, SGA-LAI patients had 46% higher adjusted odds of persistence (no gap ≥ 60 days), while FGA-LAI patients were not significantly different.
PO vs. LAI  Literature review

Treatment patterns in Medicaid patients with schizophrenia initiated on a first- or second-generation long-acting injectable versus oral antipsychotic.\textsuperscript{[19]}

Conclusion
Medicaid patients initiated on SGA-LAI demonstrated better treatment adherence and persistence compared to OAP patients, while those initiated on FGA-LAI did not show significant improvement in adherence or persistence and had more AP polypharmacy relative to OAP patients.
References


References


References


References


References

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18. Noam Y. Kirson, PhD; Peter J. Weiden, MD; Sander Yermakov, MS; Wayne Huang, MPP; Thomas Samuelson, BA; Steve J. Offord, PhD; Paul E. Greenberg, MS, MA; and Bruce J. O. Wong, MD. Efficacy and Effectiveness of Depot Versus Oral Antipsychotics in Schizophrenia: Synthesizing Results Across Different Research Designs. J Clin Psychiatry 2013;74(6):568-575
Questions?
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