Updates on the Use of Long-Acting Injectable Antipsychotics in the Treatment of People with Schizophrenia

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Outline of Presentation

1. The Role of Long-Acting Injectables (LAIs) in Antipsychotic Polypharmacy
   - What is the efficacy evidence
   - What is the safety evidence?
2. LAI Use in the Treatment of First Episode Schizophrenia
3. New LAI Formulations

1. The Role of LAIs in Antipsychotic Polypharmacy

- Antipsychotic Polypharmacy
  - 20-40% of people with schizophrenia are treated with two or more antipsychotic medications
  - There is emerging evidence that antipsychotic polypharmacy may offer some advantages to antipsychotic monotherapy
    - Decreased hospitalization rate (Katona et al, 2014; Tiihonen et al, 2019, but see Weiser et al, 2021)
    - Decreased time to all-cause antipsychotic discontinuation (Tiihonen et al, 2017, but see Tiihonen et al, 2019)

1. The Role of LAIs in Antipsychotic Polypharmacy

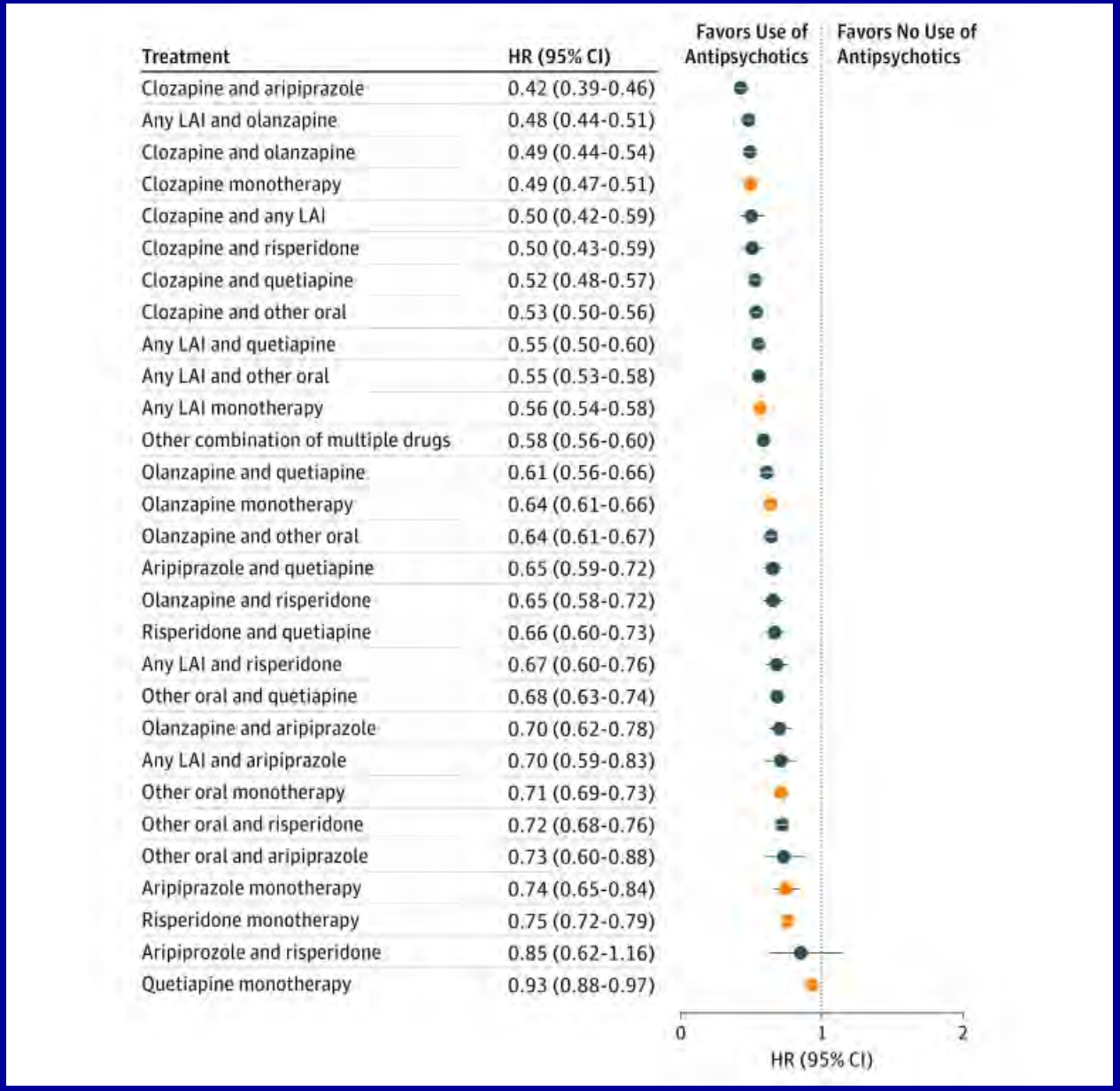
- Antipsychotic Polypharmacy (contd.)
  - Secondary to concerns about adverse events, antipsychotic polypharmacy is not a recommended treatment
  - However, there is emerging evidence that antipsychotic polypharmacy may have similar long-term risks compared to antipsychotic monotherapy
    - Comparable risk of mortality (Baandrup et al, 2010; Tiihonen et al, 2012)
    - Decreased mortality rate (Katona et al, 2014)

1. The Role of LAIs in Antipsychotic Polypharmacy

- Antipsychotic Polypharmacy (contd.)
  - LAIs are primarily recommended for people who are partially or non-adherent to their prescribed medications
  - What is their role in antipsychotic polypharmacy?
    - Tiihonen et al, 2019
    - Taipale et al, 2023

1. The Role of LAIs in Antipsychotic Polypharmacy

Risk of Psychiatric Rehospitalization During Specific Treatments Compared With No Antipsychotic Use in the Prevalent Cohort (Within-Individual Analysis)



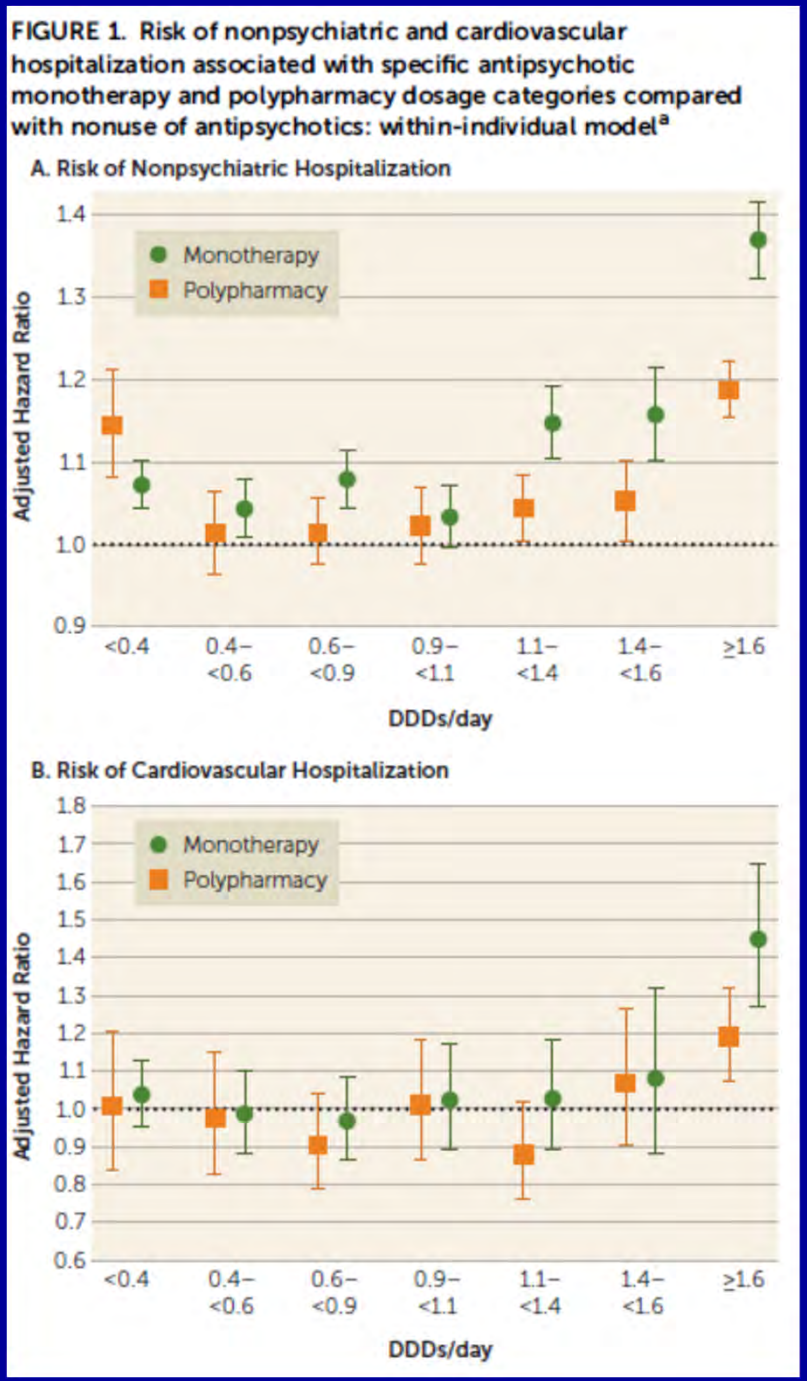
Treatment	HR (95% CI)
Clozapine and aripiprazole	0.42 (0.39-0.46)
Any LAI and olanzapine	0.48 (0.44-0.51)
Clozapine and olanzapine	0.49 (0.44-0.54)
Clozapine monotherapy	0.49 (0.47-0.51)
Clozapine and any LAI	0.50 (0.42-0.59)
Clozapine and risperidone	0.50 (0.43-0.59)
Clozapine and quetiapine	0.52 (0.48-0.57)
Clozapine and other oral	0.53 (0.50-0.56)
Any LAI and quetiapine	0.55 (0.50-0.60)
Any LAI and other oral	0.55 (0.53-0.58)
Any LAI monotherapy	0.56 (0.54-0.58)
Other combination of multiple drugs	0.58 (0.56-0.60)
Olanzapine and quetiapine	0.61 (0.56-0.66)
Olanzapine monotherapy	0.64 (0.61-0.66)
Olanzapine and other oral	0.64 (0.61-0.67)
Aripiprazole and quetiapine	0.65 (0.59-0.72)
Olanzapine and risperidone	0.65 (0.58-0.72)
Risperidone and quetiapine	0.66 (0.60-0.73)
Any LAI and risperidone	0.67 (0.60-0.76)
Other oral and quetiapine	0.68 (0.63-0.74)
Olanzapine and aripiprazole	0.70 (0.62-0.78)
Any LAI and aripiprazole	0.70 (0.59-0.83)
Other oral monotherapy	0.71 (0.69-0.73)
Other oral and risperidone	0.72 (0.68-0.76)
Other oral and aripiprazole	0.73 (0.60-0.88)
Aripiprazole monotherapy	0.74 (0.65-0.84)
Risperidone monotherapy	0.75 (0.72-0.79)
Aripiprozole and risperidone	0.85 (0.62-1.16)
Quetiapine monotherapy	0.93 (0.88-0.97)

Tiihonen et al, JAMA Psych, 2019

1. The Role of LAIs in Antipsychotic Polypharmacy

- Taipale et al examined the relative safety and efficacy of similar doses of antipsychotic monotherapy and polypharmacy within the same individual
- Three outcome measures:
  - Risk of Nonpsychiatric Medical Hospitalization
  - Risk of Cardiovascular Hospitalization
  - Risk of Psychiatric Hospitalization

1. The Role of LAIs in Antipsychotic Polypharmacy



Taipale et al, Am J Psych, 2023

1. The Role of LAIs in Antipsychotic Polypharmacy

TABLE 3. Risk of nonpsychiatric and cardiovascular hospitalization associated with polypharmacy compared with the same dosage of monotherapy use[a]

	Nonpsychiatric Hospitalization			Cardiovascular Hospitalization		
Dosage Category (DDDs/day)	Adjusted Hazard Ratio	95% CI	p	Adjusted Hazard Ratio	95% CI	p
<0.4	1.07	1.01–1.13	0.0207	0.97	0.81–1.16	0.7477
0.4–<0.6	0.97	0.92–1.02	0.2771	0.99	0.83–1.18	0.8901
0.6–<0.9	0.94	0.90–0.98	0.0038	0.93	0.80–1.09	0.3789
0.9–<1.1	0.99	0.94–1.04	0.6599	0.99	0.82–1.19	0.8989
1.1–<1.4	0.91	0.87–0.95	<0.0001	0.86	0.72–1.02	0.0893
1.4–<1.6	0.91	0.86–0.96	0.0015	0.99	0.78–1.26	0.9250
≥1.6	0.87	0.84–0.89	<0.0001	0.82	0.72–0.94	0.0035

[a] From the within-individual model. DDD=defined daily dose.

Taiplae et al, Am J Psych, 2023

1. The Role of LAIs in Antipsychotic Polypharmacy

- Taipale et al
  - In comparisons between comparable doses of antipsychotic polypharmacy and monotherapy, polypharmacy was associated with decreased risk of psychiatric hospitalizations at lower and higher dosages
  - Caveats:
    - Taipale et al and other reviewed studies are all observational studies based on utilization of large databases
      - Not feasible to conduct long-term randomized clinical trials
      - The data utilized were not collected to address the specific questions asked in these studies
    - Taipale et al and other studies did not examine the relative occurrence of less seriously side effects (e.g., EPS, sedation, diminished mental acuity)

1. The Role of LAIs in Antipsychotic Polypharmacy

- Implications:
  - The use of an LAI in antipsychotic polypharmacy may offer efficacy and safety advantages for those who have not responded to antipsychotic monotherapy
    - The use of LAIs may result in lower plasma levels than the comparable dosage of an oral formulation, which could account for the enhanced safety
  - Rational Polypharmacy
    - In other fields of medicine, treatment guidelines frequently recommend the concurrent use of medications with different mechanisms of action to improve treatment response
    - The delineation of the mechanism of action of antipsychotic combinations that are associated with optimal therapeutic response would be critical for identifying other combinations and the development of novel antipsychotic agents

2. LAI Use in the Treatment of First Episode Schizophrenia

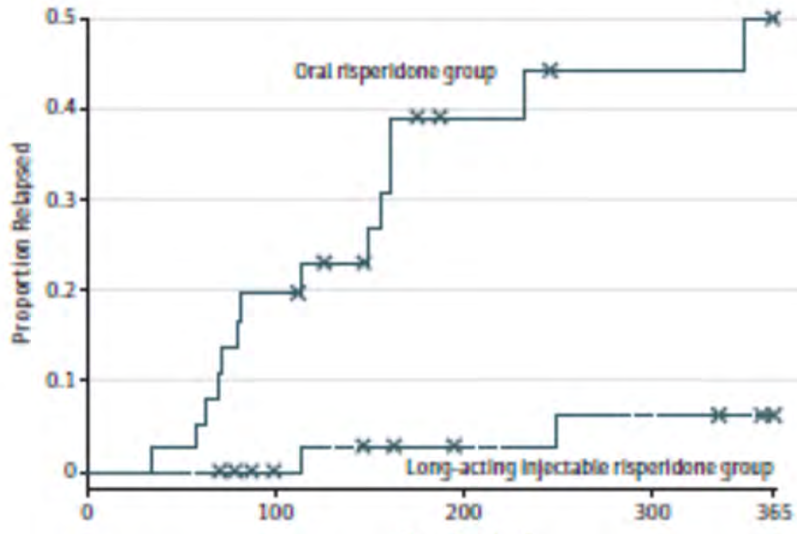
- People who are experiencing a first episode of psychosis often struggle with medication adherence
  - "Why do I need to take these medications when I am feeling better"
  - "I do not like the way the medications make me feel (e.g. sedated, foggy, sexual side effects)"
  - "It is a nuisance to have to take these medications every day"
- In response to concerns about adherence, several studies have examined the efficacy and safety of LAIs in this population (mostly risperidone and paliperidone LAI formulations)

2. LAI Use in the Treatment of First Episode Schizophrenia

- Subotnik et al examined the comparative efficacy and safety of risperidone LAI versus oral risperidone (JAMA Psychiatry 2015)
  - 12-month RCT
  - Participants were stabilized on 3 weeks of oral risperidone then randomly assigned to oral vs LAI risperidone
  - Primary Outcome measure:
    - Positive symptom exacerbation
  - Secondary Outcome measures:
    - Psychiatric hospitalizations
    - Positive symptom control (% of time symptoms were of mild severity)
    - Medication discontinuation

2. LAI Use in the Treatment of First Episode Schizophrenia

Figure 2. Time to First Psychotic Exacerbation and/or Relapse as a Function of Form of Medication Administration in 83 Patients



No. of patients					
Oral risperidone group	43	32	30	30	18
Long-acting injectable risperidone group	40	35	30	29	28

The risk of exacerbation and/or relapse over time was significantly lower for the long-acting injectable risperidone group than for the oral risperidone group. x Indicates censored data.

Two of 40 (5%) LAI participants experienced a psychotic sx exacerbation vs 14 of 43 (33%) in the oral risperidone group; $X^2=11.1$, $p<0.001$

Subotnik et al, JAMA Psychiatry 2015

2. LAI Use in the Treatment of First Episode Schizophrenia

Subotnik et al (JAMA Psychiatry 2015)

– Secondary Outcome measures:

- Psychiatric hospitalizations: 2 of 40 (5%) LAI participants experienced hospitalization versus 8 of 43 (19%) in the oral risperidone group; X^2=3.8, p=0.05
- Positive symptom control: Risperidone LAI was associated with longer periods of reduction in hallucinations and delusions (β=-0.30; t=-2.6; p=0.01)
- Medication discontinuation: there were no significant differences in drug discontinuation because of adverse events between the two groups (risperidone LAI: 10%; oral risperidone: 21%, p=0.14)

2. LAI Use in the Treatment of First Episode Schizophrenia

Table 2. Adverse Effects of Oral vs Long-Acting Injectable Risperidone

	Oral Risperidone[a]		Long-Acting Injectable Risperidone[a]	
Adverse Effect Variable	Baseline	End Point	Baseline	End Point
Akathisia				
Severity, mean (SD)[b]	0.2 (0.8)	0.4 (0.8)	0.3 (0.5)	0.2 (0.4)
Proportion rated ≥2, %	5.9	3.3	0	0
Proportion rated ≥3, %	2.9	3.3	0	0
Involuntary movements				
Severity, mean (SD)[c]	0.2 (0.6)	0.1 (0.4)	0.0 (0.0)	0.03 (0.2)
Proportion rated ≥2 on any item, %	5.9	10.0	0	0
Proportion rated ≥3 on any item, %	0	3.3	0	0
BMI, mean (SD)	27.0 (5.5)	28.3 (6.7)	28.8 (5.1)	30.8 (6.1)
Total cholesterol level, mean (SD)	179.7 (5.8)	171.9 (7.0)	179.4 (5.9)	177.9 (6.6)
Hemoglobin A_{1c} level, mean (SD)	5.3 (0.3)	5.3 (0.3)	5.4 (0.7)	5.7 (1.3)
Prolactin level, mean (SD)	57.3 (41.7)	41.6 (22.8)	56.8 (36.3)	36.0 (18.6)
Blood pressure, mean (SD), mm Hg				
Systolic	111.1 (10.0)	117.2 (11.6)	112.7 (12.3)	119.2 (11.4)
Diastolic	70.9 (7.2)	72.5 (11.5)	71.9 (8.5)	75.9 (7.1)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01; prolactin to picomoles per liter, multiply by 43.478.

[a] No change in score differences between groups were significant at $P < .05$.

[b] The severity item of the Barnes Rating Scale for Akathisia is rated on a scale from 0 (absent) to 5 (severe akathisia).

[c] The Abnormal Involuntary Movement Scale items are rated on a scale of 0 (none) to 4 (severe).

Subotnik et al, JAMA Psychiatry, 2015

2. LAI Use in the Treatment of First Episode Schizophrenia

- Conclusions
  - Although not all studies that have examined the comparative efficacy of LAIs versus oral antipsychotics have demonstrated such pronounced benefits, the majority of studies support the efficacy benefit of LAIs, especially with regard to reducing relapse and re-hospitalization rates
  - LAIs may also be associated with improved symptom response, increased remission rates, and improved adherence
  - In combination, the results of these studies strongly support the increased utilization of LAIs in the treatment of people with a first episode of psychosis

3. New Formulations

- Over the past 10-15 years, a number of LAI formulations of second generation antipsychotics have been developed.
- The different formulations offer flexibility in frequency and route of administration
  - Aripiprazole
    - Abilify Maintena: 400mg IM/month
    - Abilify Asimtufil: 960 mg IM q2 months
    - Aristada: may be administered IM q month, q6 weeks, or q2 months (depending on dose)
  - Olanzapine
    - Zyprexa Relprevv: may be administered IM q2 weeks or q month (depending on dose)

3. New Formulations (contd.)

- Paliperidone
  - Invega Sustenna: choice of three different doses, which are administered IM q month
  - Invega Trinza: choice of three different doses, which are administered IM q3 months
  - Invega Hafyera: choice of two different doses, which are administered IM q6 months
- Risperidone
  - Risperdal Consta: choice of three different doses, which are administered IM q2 weeks
  - Rykindo: 25 mg IM q2 weeks
  - Perseris: choice of two doses, which are administered ***SC*** q month
  - Uzedy: may be administered ***SC*** q month or q2 months (depending on dose)

Conclusions

1. There is increasing evidence to support the efficacy and safety of LAIs in antipsychotic polypharmacy
2. LAIs should be considered in the first line treatment of people with a first episode of schizophrenia
3. There are multiple LAI formulations, which provide flexibility on the frequency and route of administration