INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Long-Acting Injectable Antipsychotics***
-April 2025-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of long-acting antipsychotic injectable (LAI) agents. Prior to this brief, the National Core Formulary (NCF) included haloperidol decanoate and aripiprazole lauroxil which were added after review in November 2020. Following clinical review and analysis, the NPTC voted to (1) **REMOVE haloperidol decanoate** from the NCF and (2) **MODIFY** the NCF to read as **"any formulation" of either long-acting, injectable aripiprazole -OR- long-acting, injectable paliperidone.**

Discussion:

In 2020, the NPTC examined the role of LAI agents in treatment of serious mental illness (SMI), specifically schizophrenia spectrum disorders and bipolar disorder. It was determined that LAI medications were essential in the treatment of SMI. Based on safety and efficacy data, clinical guidelines and market analysis, haloperidol decanoate (first generation antipsychotic) and aripiprazole lauroxil (second generation antipsychotic) were added to the NCF.

SMI affects roughly 14.6 million people in the US with higher rates among American Indian and Alaska Native (AI/AN) people.[1] The prevalence of SMI in 2023 was 7.3% among AI/AN people and rates of suicide in this group was 50% higher than for non-Hispanic white people.[2,3] Six agents with multiple formulations were examined in this review: aripiprazole (monohydrate and lauroxil), fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, and risperidone (microspheres and subcutaneous injection). Sub-formulations differ in frequency of administration, for example aripiprazole monohydrate has an every 4-week and an every 2-month formulation. Similarly, paliperidone palmitate has three formulations: monthly, every 3-month, and every 6-month administration. Longer duration of action is key in LAI superiority over oral medications in SMI. Schizophrenia and bipolar disorder are accompanied by symptoms which prevent patients from regularly engaging in care and taking daily medications.

LAIs have superior efficacy in rates of relapse and hospitalization in patients with schizophrenia.[4] A retrospective longitudinal cohort study of Medicaid claims in South Carolina showed that patients treated with LAIs had more consistent 'days covered' with medication and had more outpatient engagement with the medical system. It also demonstrated that, excluding medication costs, outpatient care was ~$2,500 cheaper than patients on oral medications. This benefit was lost when factoring in medication cost.[5] Patients treated with LAIs have improved morbidity and mortality compared with oral treatment and the increased time under treatment with LAIs preserves brain volume thus mitigating long term cognitive decline associated with poorly controlled schizophrenia.[6,12] In head-to-head analysis of all commercially available LAIs (including haloperidol decanoate), meta-analysis showed only paliperidone (every 3-months, every 1-month) and aripiprazole (any formulation) demonstrated decreased risk of relapse (Adjusted HR 0.81, 95% CI: 0.79-0.84).[9]

Safety and efficacy of LAIs have been compared to both placebo and oral antipsychotics. An industry-funded study demonstrated both increased persistence and lower risk for negative outcomes with LAIs. Paliperidone palmitate every 3-month dosing was found to have the lowest discontinuation rates, hospitalization rates and treatment failures (33-47% lower risk) compared with oral risperidone, LAI risperidone, LAI aripiprazole (every 1 month) and LAI haloperidol (every 1 month).[7] In a head-to-head meta-analysis of LAI efficacy and tolerability, aripiprazole had the highest rates of acceptability followed by paliperidone (3-month and 1-month formulations), aripiprazole, and olanzapine supported by moderate-to-high certainty of evidence in prevention of relapse, patient acceptability, efficacy and tolerability.[8]

The American Psychiatric Association (APA) clinical guidelines recommend use of LAIs in patients who prefer long-acting treatment or those who struggle to adhere to oral medication regimens (2B recommendation).[10] The World Psychiatric Association recommend that LAIs can be beneficial in early phases of schizophrenia and, in an independent meta-analysis recommended aripiprazole, olanzapine and paliperidone as the best choices for maintenance therapy.[11]

Clinical use of these medications should be guided by trained prescribers in psychiatric care. Typical use requires initiation with oral medications prior to use of LAI to ensure efficacy, tolerability, and monitoring of side effects. Transition from oral to injectable treatment has been simplified since our last review and details can be found in any current prescribing reference. That said, oral-to-injectable transition must be among 'like-drugs', for example, oral aripiprazole can only be converted to injectable aripiprazole. However, paliperidone is a metabolite of risperidone, thus oral risperidone or oral paliperidone may both be converted to injectable paliperidone without additional medication adjustments.

Agency utilization review showed changing trends in prescribing since 2020. Use of haloperidol decanoate has significantly decreased in line with clinical practice. Conversely, use of paliperidone has increased likely in response to data demonstrating improved efficacy and tolerability and ease of transition from oral risperidone, which is a commonly used oral antipsychotic across the agency. Utilization of risperidone LAI has not significantly changed, likely due to a less favorable side effect profile. Use of both aripiprazole monohydrate and lauroxil are similar, with the monohydrate formulation carrying an FDA approval for use in both schizophrenia and bipolar disorder while lauroxil is only approved for schizophrenia treatment. Cost-efficacy of aripiprazole monohydrate and lauroxil is comparable.

Findings:

LAI agents were found to be efficacious, tolerable and safe for the treatment of schizophrenia and bipolar disorder, moreover the adherence and persistence of these drugs in treating challenging mental illness is superior to oral formulations. LAIs improve patient engagement in care and, while upfront drug costs can be greater, outpatient care costs are lower. Agency utilization data pointed to decreased utilization of haloperidol decanoate and increasing utilization of paliperidone palmitate, likely due to ease of transition from commonly used oral formulations. Cost-efficacy of aripiprazole formulations has equalized since our last review and, given the additional FDA approval of aripiprazole monohydrate for use in bipolar disorder, formulation specification was removed from the NCF. Thus, following clinical review and analysis, the NPTC voted to (1) remove haloperidol decanoate from the NCF and (2) modify the NCF to read as “any formulation” of either long-acting, injectable aripiprazole -OR- long-acting, injectable paliperidone.

Please note that changes to the National Core Formulary do not preclude appropriate clinical planning and decision making for individual patients. The NPTC recommends patient-centered and clinically based discussions when making any changes to an individual’s medications.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References

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