INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Oral Atypical Antipsychotics*
-April 2025-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of oral atypical antipsychotics. This class of medications was most recently reviewed by the NPTC in 2022 for bipolar disorder. The IHS National Core Formulary (NCF) currently lists atypical antipsychotics (any product), requiring facilities to maintain any one of such agents on local formulary but deferring the selection of the specific agent to the discretion of the facility. Following clinical review and analysis, the NPTC made **no modifications** to the NCF.

Discussion:

Antipsychotic medications are the cornerstone treatment for schizophrenia, a chronic, relapsing psychotic disorder affecting nearly 1% of the global and IHS user population.[1,2] In 1989, clozapine was the first atypical (or second-generation) antipsychotic approved in the United States (U.S.) by the Food and Drug Administration (FDA) for the treatment of schizophrenia. Atypicality referred to the limited risk for extrapyramidal side effects that were characteristic of the typical (or first-generation) antipsychotic agents.[3] Since the approval of clozapine, 15 atypical antipsychotics have been FDA approved for the treatment of various psychiatric conditions, including schizophrenia, bipolar disorder, major depressive disorder, Parkinson disease psychosis, irritability in autism and agitation in dementia.[4]

As a class, atypical antipsychotics are efficacious for the treatment of various psychiatric conditions, namely psychotic disorders. Atypical antipsychotics have a number needed to treat of 6 and 3 for the acute and maintenance treatment of schizophrenia, respectively.[5] Meta-analytic data have failed to demonstrate differences in the efficacy of antipsychotics for both the acute and maintenance treatment phases of schizophrenia, or across subgroups of patients.[6,7] A systematic review and network meta-analysis comprising over 53,000 adults with schizophrenia comparing 32 oral antipsychotics in the acute treatment of schizophrenia found that all antipsychotics reduced overall symptoms more than placebo, with standardized mean differences (SMD) ranging from -0.89 (95% CrI: -1.08 to -0.71) to -0.03 (95% CrI: -0.59 to 0.52).[6] Similarly, a follow up meta-analysis and network meta-analysis comprising over 18,000 adults with schizophrenia comparing 32 oral and long-acting injectable antipsychotics in the maintenance treatment of schizophrenia found that all antipsychotics had risk ratio (RR) <1.00 compared with placebo for relapse prevention (RRs ranged from 0.2 (95% CrI 0.05–0.41) for to 0.65 (0.16-1.14).[7] Both analyses found wide variability in side effect profiles of medications (see table), indicating that drug choice should be guided by tolerability.[6,7]

Medication	Weight gain	Glucose abnormalities	Hyperlipidemia	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Prolactin elevation	Sedation	Anticholinergic	Orthostatic hypotension	QTc prolongation
Second-generation agents												
Aripiprazole	+	+	+	++	+	+	+	+	+	+	+	*
Asenapine	++	++	++	++	++	++	++	++	++	+	++	*
Brexpiprazole	++	++	++	+	++	+	+	++	++	+	+	×
Cariprazine	+	+	+	+++	++	++	+	+	+	+	+	×
Clozapine	+++	+++	+++	+	+	+	++	+	+++	+++	+++	*
Iloperidone	++	++	++	++	++	++	++	++	++	+	+++	++
Lumateperone	+	+	+	+	+	+	+	+	++	+	+	*
Lurasidone	+	+	+	+++	++	++	++	++	+	+	+	*
Olanzapine	+++	+++	+++	++	++	++	++	+	+++	+	++	*
Paliperidone	++	++	++	++	+++	++	++	+++	++	+	++	++
Pimavanserin	0	0	0	0	0	0	0	0	+	+++	0	0
Quetiapine	++	++	++	+	+	+	++	+	+++	++	++	*
Risperidone	++	++	++	++	+++	++	++	+++	++	+	++	++
Ziprasidone	+	+	+	++	++	++	++	++	++	+	++	+++
Other antipsychotic medications												
Xanomeline-trospium	0	0	0	0	0	0	0	0	+	+++	0	0

Adapted from Muench J, Hamer AM. Second-generation and other antipsychotic medications: pharmacology, administration, and side effects. UpToDate. Updated April 23, 2025. Available from: https://www.uptodate.com/contents/second-generation-and-other-antipsychotic-medications-pharmacology-administration-and-side-effects

Lumateperone and xanomeline-trospium are the most recently approved FDA medication for the treatment of schizophrenia (and bipolar depression, in the case of lumateperone) and were not included in the above meta-analyses. A 2024 meta-analysis of 7 randomized controlled trials (RCT) found that lumateperone was efficacious in reducing depressive symptoms in bipolar depression (SMDs -0.36, 95% CI: -0.59 to -0.13) and demonstrated a lower combined SMD of -0.14 (95% CI: -0.27 to 0, p=0.051, I^2 = 49.6%) in treatment of schizophrenia, showing no significant difference from the placebo group in the latter case, although the p-value approached significance. The lumateperone group did demonstrate significantly higher response rates compared with placebo in bipolar depression (RRs 1.27, 95% CI: 1.07 to 1.51) and schizophrenia (RRs 1.44, 95% CI: 1.12 to 1.86).[8] Treatment-emergent adverse events included somnolence, dry mouth, dizziness, nausea, and headache (RRs 1.30 to 3.29); however, lumateperone did not significantly increase extrapyramidal symptoms (RR 1.46, 95% CI: 0.84 to 2.53). A 2025 meta-analysis of 3 RCTs found that xanomeline-trospium led to a greater change from baseline in Positive and Negative Syndrome Scale for schizophrenia (PANSS) total score (MD -13.17, 95% CI: -20.16 to -6.18; p= 0.0002; I^2 = 100%). Xanomeline-trospium was associated with the occurrence of cholinergic adverse events, including nausea (18.5% vs. 3.8%; RR 4.37, 95% CI: 2.43 to 7.84; p<0.000001; I^2 = 19%) but was not associated with akathisia (MD -0.00; 95% CI: -0.13 to 0.13; p=0.9; I^2 = 0%) or weight gain (MD -0.36; 95% CI: -1.18 to 0.46; p=0.38; I^2 = 51%).[9] Therefore, both medications demonstrated a unique tolerability profile.

Recommendations across schizophrenia clinical practice guidelines reflect that an evidence-based ranking of antipsychotics is difficult due to heterogenous data. Nearly 80% (15/19) of such clinical practice guidelines, including those from the American Psychiatric Association and U.S. Veterans Affairs/Department of Defense state that physicians and their patients should discuss decisions about the choice of antipsychotic and that this decision should consider individual patient factors and preferences, risks of adverse and metabolic effects, and symptom patterns.[10] All practice guidelines recommend clozapine for treatment-resistant schizophrenia.[10]

Findings:

The IHS National Core Formulary currently lists atypical antipsychotics as “any product.” The currently available data indicate that there is no definitive evidence that any one antipsychotic is more efficacious than another (with the exception of clozapine for treatment-resistant schizophrenia) and that side effect profiles vary greatly. Clinical guidelines therefore support shared decision making in antipsychotic choice, which is consistent with the heterogenous prescribing pattern of this drug class across the IHS. Ultimately, the NPTC made no modifications to the National Core Formulary.

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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