Rethinking Amisulpride:

Could *N*-Methylation Result in a New and Even Better Antipsychotic?

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At the American Society of Clinical Psychopharmacology (ASCP) meeting in May 2025[1] and European College of Neuropsychopharmacology (ECNP) meeting in October 2025,[2,3] important new phase 2 data were presented on LB-102, an *N*-methylated analogue of the antipsychotic amisulpride, and currently under development for the acute treatment of schizophrenia and other neuropsychiatric illnesses.[4] In that context, we consider it useful for clinicians in the US to become more familiar with amisulpride's history and data, and the rationale behind the development of (yet to be named) LB-102.

Amisulpride is a second-generation antipsychotic that is a substituted benzamide derivative and was developed in France in the 1980s. Amisulpride is currently approved for psychiatric indications, including schizophrenia, in over 50 countries worldwide. However, approval for the treatment of schizophrenia was never sought in the US. Amisulpride, more specifically, its *S*-enantiomer, is a specific dopamine receptor antagonist with high and similar affinity for the dopamine D_2 and D_3 receptors.[4] Amisulpride is highly efficacious and well tolerated with few motor side effects.[5] Amisulpride's low potential for neuromotor side effects despite minimal 5-HT_{2A} antagonism has been explained by in vivo demonstrated "limbic selectivity" and preferential antagonism at dopamine D_2/D_3 autoreceptors at low doses, which may increase dopamine transmission, thereby possibly explaining efficacy of amisulpride for negative symptoms at lower doses (ie, 50-300 mg/day) and positive symptoms at higher doses (ie, 400-800 mg/day, max. 1200 mg/d, twice daily if >400 mg/day).[6] Given some efficacy of antidepressants for negative symptoms in schizophrenia,[7] negative symptom benefits of amisulpride[8] may further be conferred by the *R*-enantiomer of amisulpride that functions as a 5-HT_7 antagonist, which has shown some promise for depression in a nonracemic mixture (85% *R*-enantiomer vs 15% *S*-enantiomer).[9]

Notably, in a network meta-analysis[5] of placebo-controlled and head-to-head randomized controlled trials (RCTs) of 32 antipsychotics involving 402 studies and including 53,463 subjects (excluding those with treatment resistance, a first episode, or predominant negative or depressive symptoms), amisulpride (effect size [ES] = 0.73) ranked in overall efficacy as second only to clozapine (ES = 0.89) and higher than olanzapine (ES = 0.56) or risperidone (ES = 0.55). Regarding positive symptom improvement, amisulpride ranked first (ES = 0.69), followed by clozapine (ES = 0.64), risperidone (ES = 0.61), and olanzapine (ES = 0.53). Additionally, a meta-analysis of 21 RCTs reported that amisulpride was the only antipsychotic outperforming placebo regarding predominant negative symptoms (albeit in lower doses than used to treat acute psychosis).[5] Additionally, in a network meta-analysis of 92 placebo- and active-controlled clinical trials published prior to 2021 (N = 22,645), the majority of the 31 included antipsychotics outperformed placebo regarding the primary outcome of relapse prevention.[10] Compared to placebo, "high" confidence in the results was found for (in descending order of ES) amisulpride oral, olanzapine oral, aripiprazole long-acting injectable (LAI), olanzapine LAI, aripiprazole oral, paliperidone oral, and ziprasidone oral. However, in these meta-analyses, RCTs involving amisulpride were mostly older and also contained more active-controlled than placebo-controlled RCTs,[10] which could potentially inflate ES. Hence, it is important to consider more contemporary RCTs. Johnsen et al[11] conducted a 1-year head-to-head RCT in 144 adults with schizophrenia with a mean Positive and Negative Syndrome Scale (PANSS) score of 78. Patients were randomized to amisulpride (50–1,200 mg/d; n = 44), aripiprazole (5–30 mg/d; n = 48), and olanzapine (2.5–20 mg/d; n = 52) and assessed by masked rater. After 52 weeks, PANSS total scores declined by 33 points with amisulpride, 22 with

aripiprazole, and 23 with olanzapine. This was a statistically and clinically significant difference favoring amisulpride, without differences in serious adverse effects.

In an open-label 1-year RCT, haloperidol was compared to second-generation antipsychotics among 498 patients aged 18–40 years with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder at 50 sites and in 14 countries. Patients were randomized to haloperidol (1–4 mg/d; n = 103), amisulpride (200–800 mg/d; n = 104), olanzapine (5–20 mg/d; n = 105), quetiapine (200–750 mg/d; n = 104), or ziprasidone (40–160 mg/d; n = 82).[10] The primary outcome, all-cause discontinuation, was highest for haloperidol (Kaplan-Meier estimate 72%), followed by quetiapine (53%) and ziprasidone (45%), and lowest for amisulpride (40%) and olanzapine (33%).[12] However, symptom reductions were virtually the same in all groups at approximately 60%. Amisulpride was generally well tolerated with lower rates of all-cause discontinuation. The adverse effect that stood out was 89% of patients on amisulpride having hyperprolactinemia, likely due to the low blood-brain barrier penetrance of amisulpride, versus 41%–50% of patients with hyperprolactinemia with the other antipsychotics ($P < .001$). However, there were no differences in spontaneously reported rates of sexual dysfunction. Prolonged electrocardiogram QTc intervals were observed in 5% of amisulpride-treated participants compared to 4% receiving olanzapine.[12]

In another, 3-phase, study conducted at 27 centers in 14 European countries and Israel, patients aged 18–40 years with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder were treated for 4 weeks with up to 800 mg/d oral amisulpride in an open-label design (phase 1).[13] Patients not meeting cross-sectional symptomatic remission criteria (as per Andreasen et al[14]) at 4 weeks were randomized to continue amisulpride or switch to olanzapine (≤20 mg/d) during a 6-week double-blind phase, with patients and staff masked to treatment allocation (phase 2). Patients who were not in remission at 10 weeks received open-label clozapine (≤900 mg/d) for an additional 12 weeks (phase 3). Of the 446 patients in the intention-to-treat sample, 371 (83%) completed amisulpride treatment, and 250 (56%) achieved remission after phase 1. Altogether, 93 patients who were not in remission continued to the 6-week double-blind switching trial, with 72 (77%) patients completing the trial (39 on olanzapine and 33 on amisulpride); 15 (45%) patients on amisulpride versus 17 (44%) on olanzapine achieved symptomatic remission ($P = .87$). Side effects were as expected, ie, in phase 1, amisulpride was associated with motor side effects and adverse effects related to increased prolactin levels. In phase 2, side effects were more prominent in the patients receiving olanzapine compared to amisulpride, especially weight gain. The authors concluded that "for most patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine. Since switching to olanzapine did not improve outcome, clozapine should be used after patients fail a single antipsychotic trial, and not until 2 antipsychotics have been tried, as is the current recommendation."[13]

In a 16-site, double-blind RCT, adults aged 18–65 years with non–first-episode schizophrenia or schizoaffective disorder and with a PANSS total score of ≥70 with ≥2 positive symptoms ≥4 were randomized to 16 weeks of treatment with amisulpride plus olanzapine (n = 110), amisulpride (200–800 mg/d; n = 109) plus placebo, or olanzapine (5–20 mg/d; n = 102) plus placebo.[15] Among the 321 analyzed patients, PANSS total score at the 8-week primary outcome time point improved significantly more in the amisulpride + olanzapine group (−29.6 ± 14.5) than in the olanzapine + placebo monotherapy group (−24.1 ± 13.4, $P = .049$, ES = 0.40 in favor of the combination treatment group). In contrast, the amisulpride + placebo monotherapy group was not statistically inferior to the amisulpride + olanzapine group (−25.2 ± 15.9, $P = .095$, ES = 0.29), supporting amisulpride's relative efficacy.[15]

Regarding tolerability, a safety review of 11 amisulpride studies documented neuromotor adverse effects similar to risperidone,[16] while a systematic review of antipsychotic side effects reported prolactin elevation and total cholesterol increase as the most prominent adverse effects for amisulpride, with low risk for all other documented adverse effects.[17] In a network meta-analysis of short-term trials in patients with acutely exacerbated schizophrenia, Huhn et al[5] reported significantly and markedly greater prolactin elevation and QTc prolongation with amisulpride compared to placebo. Additionally, amisulpride had somewhat greater effects than placebo on body weight (0.84 kg, 95% CI = 0.14–1.54) and akathisia, without significant difference from placebo regarding use of anticholinergic medications, sedation, and anticholinergic side effects.[5]

The development of LB-102, a methylated analogue of amisulpride, which functions as both a dopamine $D_{2/3}$ and 5-HT_7 antagonist,[18] was intended to improve upon the poor blood-brain permeability of amisulpride, while retaining the efficacy for total, positive, and, potentially, negative symptoms, and also limiting peripheral adverse effects due to a smaller periphery-to-central drug level gradient and thus lower total doses of LB-102 being needed. The *N*-methyl amisulpride (LB-102) produced similar or superior

behavioral responses in animal models at significantly lower doses than amisulpride, which itself required 630–910 mg/d to achieve 70%–80% postsynaptic striatal D2 receptor occupancy in humans.[19] LB-102's pharmacologic difference from amisulpride, with much higher blood-brain barrier penetrance, results in a lower frequency of prolactin elevation, as the pituitary gland is outside the blood-brain barrier. Similarly, QTc prolongation would also be expected to be less likely with the lower doses required for LB-102.

In healthy volunteers, once-daily dosing of LB-102 as low as 50 mg for 4 days produced 60%–80% dopamine D_2 striatal occupancy,[20] and the phase 1 dose-finding study in 64 volunteers identified a target dose range of 50–100 mg.[21] In the subsequent phase 2 study, 359 adults (aged 18–55 years) with acute schizophrenia were randomly assigned 3:3:1:3 to LB-102 50 mg/d, 75 mg/d, or 100 mg/d (with the 100-mg dose being considered exploratory) or placebo for 4 weeks.[1] All LB-102 doses were statistically superior to placebo in reducing PANSS total score at 4 weeks, with reported ES of 0.61 for 50 mg/d LB-102, 0.41 for 75 mg/d, and 0.83 for 100 mg/d.[1] The most common adverse effects were insomnia, headache, anxiety, and agitation.[1] Low rates of neuromotor side effects (1.0%, 5.6%, and 5.6% in the 50-mg, 75-mg, and 100-mg cohorts, respectively) and somnolence (0.9%, 3.7%, and 5.6% in the 50-mg, 75-mg, and 100-mg cohorts, respectively) were observed.[2] Treatment-emergent adverse events of "hyperprolactinemia" (sum of the preferred terms "hyperprolactinemia" and "blood prolactin increased") were reported in 11 participants (10.3%) in the LB-102 50-mg group, 8 (7.4%) in the 75-mg group, and 6 (16.7%) in the 100-mg group.[1] Reported potentially prolactin-related adverse events occurred in 5 patients (2.0%) and included galactorrhea (50 mg: n = 2; 75 mg: n = 1), breast enlargement (100 mg: n = 1), and erectile dysfunction (100 mg: n = 1).[1] Regarding QTc, no patient in the phase 2 trial met the prespecified stopping criteria related to QTcF prolongation, which was defined as an increase >60 ms or an absolute QT interval >500 ms.[3]

Taken together, these findings suggest that amisulpride possesses some unique characteristics among available antipsychotic agents and that the *N*-methylated analogue of amisulpride, LB-102, could be a valuable addition to the therapeutic armamentarium for treating schizophrenia. Further studies are underway.

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