

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Clozapine augmentation with amisulpride

A 42-year-old man with treatment-resistant schizophrenia presented a progressive clinical worsening under clozapine treatment (450 mg/d). He experienced worsening auditory hallucinations, increased distress and decreased working and social functioning (Positive and Negative Syndrome Scale [PANSS] score 97; positive subscale 21; negative subscale 31; general subscale 45). He experienced several side effects: drooling, daily sedation, orthostatic hypotension. We considered an add-on of up to 6 mg/d of haloperidol as a first approach. There was no clinical response within 3 months; the patient stopped working and ceased social interactions. Furthermore, after adding haloperidol, treatment tolerability worsened: the patient reported sexual side effects and extrapyramidal symptoms. Treatment augmentation was gradually switched from haloperidol to up to 1000 mg/d of amisulpride. This strategy resulted in clinical improvement, which allowed the patient to return to work and to his usual social activities (PANSS score after 2 months 69; positive subscale 17; negative subscale 20; general subscale 32). Following the switch to amisulpride, treatment tolerability improved.

Antipsychotic treatments are not effective for 5%–25% of patients with schizophrenia.¹ For these patients, all international guidelines suggest clozapine as the treatment of choice. Unfortunately, it has been reported that 40%–70% of treatment-resistant patients do not respond to clozapine.² In these patients, who are considered to have super refractory schizophrenia (SRS), augmentation strategies must be considered.³ Unfortunately, evidence supporting augmentation strategies has been weak, and there is no overall

accepted recommendation. The largest meta-analysis to date showed a small overall effect of clozapine augmentation with second-generation antipsychotics (SGAs).⁴ Therefore, it is still impossible to develop an algorithm or treatment schedule options for patients with SRS. International guidelines report only some treatment options for SRS and avoid any hierarchical order. However, increasing evidence on the efficacy of some augmentation strategies in a subgroup of patients with SRS may assist clinicians to choose the best individual treatment. For example, in patients with persistent positive symptoms, the usefulness of adding risperidone, haloperidol, olanzapine or aripiprazole has been supported.³ However, aripiprazole aside, these add-on therapies were associated with lower tolerability. Another option is augmentation with amisulpride,^{5,6} which has been reported to be effective and well tolerated.

Amisulpride preferentially binds to dopamine (DA) D2/D3 receptors in limbic rather than striatal structures, and it has low affinity for the DA D1, D4 and D5 receptor subtypes. It also acts on several other receptors that are not involved directly in the dopaminergic system (e.g., serotonin, histamine H1, α -adrenergic and β -adrenergic receptors).⁷ Concerning serotonergic activity, amisulpride has high affinity antagonism for 5-HT_{2B} and agonism for 5-HT₇.⁸ These features result in fewer extrapyramidal side effects, sedation and anticholinergic effects than first-generation antipsychotics (FGAs). Compared with SGAs, amisulpride is more likely to cause hyperprolactinaemia, but it has less risk of weight gain and does not seem to be associated with diabetogenic effects. Regarding cardiac side effects, a risk of torsade de pointes has been demonstrated with amisulpride overdose, but the risk of QTc prolongation at therapeutic dos-

ages has been classified as low.⁹ Further, although the activity on 5-HT_{2B} has been associated with valvular heart disease, this side effect was associated with 5-HT_{2B} agonism rather than antagonism, as in the case of amisulpride.¹⁰

Amisulpride augmentation was used mainly for the persistence of negative symptoms in patients with SRS. The mechanisms at the basis of its effect on negative symptoms are still debated,¹¹ but may be due in part to agonism on 5-HT₇.⁸ On the other hand, augmentation with 400–800 mg/d has shown good efficacy on positive symptoms. It could be hypothesized that patients with SRS have a more complex pathophysiology than patients who respond to FGAs or SGAs¹²; thus, they may benefit from a multisite receptor effect (like the effect of amisulpride) rather than a stronger antidopaminergic effect.¹³ Systems other than the dopaminergic one are likely involved in the pathophysiology of SRS and may represent the target of augmentation strategies.

Current knowledge about the efficacy of clozapine augmentation strategies is still poor and does not allow the development of an overall accepted evidence-based treatment algorithm. Until consensus is reached, a large number of case reports and preliminary studies may help clinicians to select the best treatment for patients with SRS based on specific psychopathological features.

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