Amisulpride:
A Useful Second-Generation Antipsychotic Omitted From the US Residency Training Curriculum

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My first experience with amisulpride was during psychiatry training in the United Kingdom in 2005. One of my clinical supervisors (who was trained in Germany) effectively used amisulpride[1] for treatment of various mental health conditions. When I moved to the United States in 2008 for my psychiatry residency, I was informed that this medication was never presented for US Food and Drug Administration (FDA) approval. Therefore, most clinicians and trainees are never taught about this drug. Amisulpride is approved and widely used in Europe and 50 other countries for schizophrenia. A recent well-designed study in Norway[2] demonstrated its superior efficacy over aripiprazole and olanzapine after 52 weeks. In 2020, amisulpride was in the news, as it was FDA approved for prevention of postoperative nausea and vomiting. At first sight, it appeared the long wait was over and finally amisulpride was available in the United States for treatment of schizophrenia. However, it is only approved and available in intravenous form for postoperative nausea and vomiting and not for any mental health indication.

Why Is Amisulpride Used in the Rest of the World?

Amisulpride is a useful second-generation antipsychotic (SGA)[3,4] that is broadly classified as a substituted benzamide. Its dosage is 400–800 mg/d divided into 2 doses; the maximum dosage is 1,200 mg/d. Amisulpride 400 mg is equivalent to 15 mg of aripiprazole or 10 mg of olanzapine. In lower doses, amisulpride binds preferentially on D_2/D_3 presynaptic autoreceptors, increasing dopaminergic transmission in the prefrontal cortex, which is linked to improvement in negative symptoms. But, at higher doses antagonism of postsynaptic dopamine receptors is understood to exert its effects in improving positive symptoms.[5] In a meta-analysis of first-episode schizophrenia spectrum disorders, amisulpride and olanzapine were found to be superior to first-generation antipsychotics (FGAs) as well as risperidone and quetiapine.[6] The efficacy of amisulpride for negative symptoms has been well established in European studies.[7,8] A Chinese study[9] replicated these findings. In another meta-analysis,[10] with the exception of clozapine, efficacy of amisulpride was similar to that of olanzapine and risperidone when compared to other FGAs. It has low risk of weight gain[11] and has moderate effects on QTc prolongation.[12] Amisulpride is not associated with diabetes mellitus[13] and is recommended for patients at risk for diabetes mellitus.[14] Amisulpride has high risk to elevate prolactin levels similar to risperidone and does not normalize even when switched with aripiprazole.[15] The prolactin increase is related to the sexual dysfunction associated with SGAs.[16] It has also been used effectively to augment clozapine[17,18] and has led to clozapine dose reduction[19] to address side effects like hypersalivation.[20,21] In combination with olanzapine,[22] it has been used as an alternative to clozapine for treatment-resistant schizophrenia.

Amisulpride is considered a drug of choice for patients with dyslipidemia, risk of diabetes, sedation, and weight gain. Amisulpride is also indicated for patients with hepatic impairments, since it is renally excreted and has minimal or no hepatic metabolism. However, it should be avoided in patients with renal impairment. There are limited data for its effectiveness in bipolar mania[23] and depression with psychotic symptoms.[24] A report[25] suggests it may lead to false positive result for buprenorphine.

Conclusion

Amisulpride is a well-established antipsychotic extensively used in rest of the world for effectively treating schizophrenia. With the dearth of antipsychotic treatment options and rising costs, there is a need to know about low-cost treatment alternatives.[26,27] Therefore, in summary there are reasons to teach residents about this medication. These include its unique psychopharmacologic profile, data supporting its efficacy in treatment, and favorable side effect profile for selected patients. Patients who visit the United States to seek second opinions may benefit from recommendations for amisulpride as an alternative to their current medications. Many US-trained psychiatrists often choose to travel and work abroad, therefore knowing about this medication will be helpful, especially when working in Europe and Australasia. Finally, being an optimist, I hope in the near future that non–industry funded trials of amisulpride get through the regulatory hurdles and that this generic drug is available for treatment of schizophrenia in the United States.

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