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MIRTAZAPINE — A MULTIFUNCTIONAL DRUG: *LOW DOSE FOR AKATHISIA*

To the Editor:

CNS Spectrums should be commended for drawing the attention of clinicians and researchers to the concept of multifunctional drugs.[1] Multifunctional drugs are agents with multiple therapeutic effects at different doses, depending upon their potency at diverse pharmacologic targets.[2] Quetiapine, trazadone, and doxepine are examples of multifunctional drugs.[1,3] Thus, quetiapine at high doses exerts dopamine $(D)_2$ and serotonin $(5\text{-}HT)_{2A}$ receptor antagonism and is used as an antipsychotic and antimanic agent. In contrast, quetiapine, like doxepine, at very low doses acts as a potent histamine $(H)_1$ receptor antagonist exhibiting robust hypnotic properties. Similarly, trazodone at low doses antagonizes $5\text{-}HT_{2A}$, H_1, and α_1-adrenergic receptors that account for its sedative and hypnotic therapeutic effects. Trazodone in doses 3–5 times higher exerts an additional inhibitory effect at the serotonin transporter and becomes an antidepressant.[3]

Mirtazapine is a widely used antidepressant and anti-anxiety medication. In therapeutic doses (range 30–90 mg/day) mirtazapine is characterized by a potent pre-synaptic α_2-adrenergic receptor blockade which accounts for its antidepressant activity. Low-dose mirtazapine predominantly antagonizes $5\text{-}HT_{2A/2C}$ and H_1 postsynaptic receptors. The preponderance of the $5\text{-}HT_{2A}$ receptor antagonism over D_2 receptor blockade was put forward as a putative explanation for the low propensity of atypical antipsychotic agents to induce extrapyramidal side effects (eg, akathisia, parkinsonism, acute dystonia).[4] Owing to its marked $5\text{-}HT_{2A}$ antagonistic properties, the addition of low-dose mirtazapine to typical antipsychotics that exert predominant D_2 receptor antagonism, was suggested to test this hypothesis. When given QD, low-dose mirtazapine (15 mg) revealed a robust anti-akathisia effect comparable to that of propranolol, the "gold standard" for akathisia,[5] mirtazapine's H_1, α_2 and $5\text{-}HT_3$ antagonistic effects are unlikely to play a role, since antihistamines, α_2 and $5\text{-}HT_3$ antagonists are apparently ineffective in the treatment of akathisia.[6] Notably, mirtazapine administered in higher doses (≥30 mg/day) may induce akathisia in susceptible individuals,[7] putatively due to stimulation of adrenergic neurotransmission via α_2 auto-receptor blockade. It seems that mirtazapine is unique in its dose-related bi-directional effect on akathisia: low doses have an anti-akathisia effect while higher doses may provoke akathisia.

The antidepressants mianserin (a structural analogue of mirtazapine) and trazodone, as well as cyproheptadine (an anti-allergy agent), that share marked $5\text{-}HT_{2A}$ antagonism at low doses, revealed anti-akathisia properties in antipsychotic-treated schizophrenia patients.[8] Notably, the effect of low-dose mirtazapine and the related compounds on antipsychotic-induced parkinsonism did not differ significantly from that of placebo, supporting the hypothesis regarding the distinct pharmacological mechanisms underlying antipsychotic-induced extrapyramidal adverse effects. Overall, the revealed robust effect of low-dose mirtazapine on antipsychotic-induced akathisia, in addition to its beneficial safety and tolerability profile, encourage modification of treatment guidelines for acute akathisia, by recommending low-dose mirtazapine along with propranolol as first-line anti-akathisia treatments.[5,9]

Mirtazapine seems to be an additional example of a multifunctional agent used as an efficacious antidepressant in the approved dose range, and an effective anti-akathisia compound at a lower dose range.

Sincerely,
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