Letter to the Editor
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A Comment on "Successful Management of Clozapine-induced Akathisia with Gabapentin Enacarbil: A Case Report"

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TO THE EDITOR

Takeshima *et al.* [1] have recently reported on an interesting case of treatment-resistant antipsychotic-induced akathisia in a middle-aged female with paranoid schizophrenia that ultimately and favourably responded to add-on gabapentin with better overall symptomatic remission by facilitating further clozapine incremental dosing. Few points are noteworthy mentioning here.

Neuroleptic akathisia has been traditionally described with conventional antipsychotics but also with second generation antipsychotics (SGAs) especially agents with D2 tenacity (aripiprazole in this case) or high-potency (paliperidone in this case). Risk factors more pertinent to SGAs have been recognized and should be ruled in/out including diagnosis of bipolar depression, substance use, palliative care settings, and smoking. None of these have been described in the case, though.

It sounds very atypical to experience akathisia on novel agents with D2 rapid dissociation and 5H2A antagonism like quetiapine and clozapine as the case illustrates. Even this is paradoxical in sense of potent anticholinergic activity that clozapine possess (M1, M2, M3 and M5 antagonism). This mandates a working differential for neuroleptic akathisia. Several subtypes of akathisia have been described; acute (less than 6 months), chronic (over 6 months), tardive (delayed onset), pseudo-akathisia (no subjective component; e.g., negative domain schizophrenia), withdrawal akathisia (discontinuation of antipsychotic), hysterical (conversion), secondary akathisia (e.g., restless leg syndrome, Vespers curse), and paradoxical akathisia (reported with benzodiazepines use). All these should be factored in given this atypical presentation. Authors, as I see, have ruled out the restless leg syndrome only.

Recalling the neurobiological underpinnings of akathisia that include D2 blockade, 5HT2A overstimulation, gamma-aminobutyric acid (GABA) deficiency, M1 cholinergic overactivity, and noradrenergic overactivity, widen the psychopharmacological armamentarium to address akathisia [2]. Unfortunately, authors first deployed the anticholinergic biperiden, whilst anticholinergic drugs are generally ineffective for akathisia. Again, to my surprise, they gave up after a trial of benzodiazepine. They combined two benzodiazepines (diazepam and clonazepam), for unknown reasons, instead of going higher with either agent. In this case, for instance, 35 mg of diazepam might be a bioequivalent total dose of this combo.

What is missing here, authors, unwittingly, did not follow the guidelines to use therapeutic options with strong evidence-base. For instance, the strongest evidence of psychopharmacotherapy to tackle neuroleptic akathisia speaks to 5HT2A antagonists and B-adrenergic blockers. I agree the latter was not an option here for the patient had bronchial asthma, but more selective agents could have been trialled. 5HT2A antagonists, like mirtazapine or cyproheptadine, allegedly a first-line option, were not trialled. Mirtazapine would have been advantageous given some data supporting a positive efficacy signal for negative domain schizophrenia. The alpha-2 agonist, clonidine, could have been of help but has not been used either. Again, clonidine would have been appealing option helping sialorrhea should higher doses of clozapine be used [3].

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Instead, authors skipped these higher evidence options to experiment with gabapentin. Gabapentin is an anticonvulsant, gabapentinoid, GABA analogue, binds selectively to alpha-2 delta-1 subunit of Ca channels that has been used in psychiatry for a multitude of indications including, inter alia, generalized anxiety disorder, restless leg syndrome, alcoholism and bipolarity [4]. Chiefly renally cleared, no pharmacokinetic interactions with antipsychotics can be theoretically expected and hence the high tolerability shown in the case. My only concern would be a resultant metabolic syndrome with this clozapine combo.

Last but not least, I can opine that gabapentin might have augmented antipsychotic response. GABA potentiation by gabapentin in theory boosts dopamine blockade in the mesolimbic pathway and attenuates serotonergic tone to the mesocortical pathway [5]. This goes hand-in-hand with hypothesized GABA deficiency underpinnings of schizophrenic neurobiology. This could mechanistically contribute to the remarkable therapeutic response in the aforementioned case. Use of gabapentin, in these clinical scenarios, is advantageous as it could also secure sleep by virtue of soporific effects and mitigate oft-time overlooked co-morbid anxiety that might signal a relapse or contribute to treatment resistance respectively.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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