

Letter to the Editor

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TO THE EDITOR:

Burke and Lincoln's letter (1) describes worsening of psychosis in a 30 year old man with undifferentiated schizophrenia when aripiprazole was added to the already prescribed haloperidol. They also discuss the possible mechanism of this worsening of psychosis which we think raises some very pertinent questions regarding management of schizophrenia (and other psychotic conditions) with partial dopamine agonists.

We have recently reported (2) on worsening of psychosis in a woman with schizo-affective disorder with addition of aripiprazole to another antipsychotic (Amisulpride) and briefly reviewed the possibility of relapse on introducing partial dopamine agonist(s) in the presence of a dopamine antagonist(s). Since cross-tapering is a common strategy used to switch between antipsychotic medications, the (short-term) co-prescription of partial dopamine agonist and dopamine antagonist is likely to be a very common clinical situation.

Aripiprazole is a high affinity, partial D₂ and 5-HT_{1A} agonist, with 5-HT_{2A} antagonist properties, and has been called as a "dopamine system stabilizer." As a partial agonist, it behaves as a functional D₂ antagonist under conditions with increased dopamine but acts as a functional D₂ agonist in presence of low dopamine concentrations. Other partial dopamine agonists include Bifeprunox, Terguride and SSR181507.

Therefore, if another antipsychotic (dopamine antagonist) is already prescribed with D₂ receptor blockade, it is expected to produce functional hypo-dopaminergia. Addition of a partial dopamine agonist (e.g., aripiprazole) at this stage allows it to act as a functional dopamine agonist, with a resultant increase in psychotic symptoms (2). The decrease in dopamine

neurotransmission caused by dopamine antagonists also leads to an up-regulation of dopamine receptors. This up-regulation can result in supersensitivity to dopamine, with or without the presence of an agonist, with the possibility of an emergent psychosis that could be treatment-resistant (2).

An up-regulation of neo-striatal receptors has been linked with emergence of tardive dyskinesia while an up-regulation of meso-limbic receptors can lead to supersensitivity psychosis (3). Supersensitivity psychosis has been reported during withdrawal from chronic antipsychotic use, including atypical antipsychotics. A supersensitive system is more liable to over-stimulation with an agonist (or a partial agonist working as a functional agonist in hypo-dopaminergic conditions). High affinity dopamine partial agonists like aripiprazole are therefore capable of causing relapse by competitively displacing the antipsychotic medication from D₂ receptors and causing over-stimulation of a supersensitive dopamine system. There are some indications from animal studies that the D₂ receptor upregulation with aripiprazole is probably less than that caused by the other high-affinity antipsychotics, like haloperidol (4). This upregulation does not seem to happen with weak D₂ blockers like clozapine, with which aripiprazole has been combined with good clinical effect (5).

Partial dopamine agonists are a useful treatment choice in schizophrenia and other psychoses, with a favorable side-effect profile. However, there appears to be a need for care in co-prescribing or cross-titrating dopamine partial agonist and antagonist treatments.² Double blind clinical trials understandably do not study polypharmacy while naturalistic studies often do not account for its effects.

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