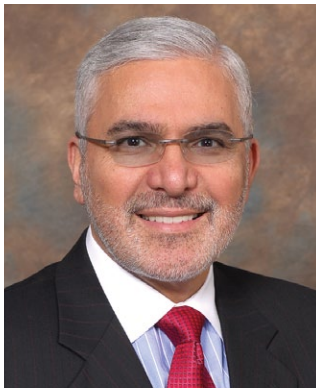

**Henry A. Nasrallah, MD**
Editor-in-Chief

# Beyond dopamine: The 'other' effects of antipsychotics

**Ask any psychiatrist how antipsychotics (APs) work and the overwhelming response will be "by blocking dopamine receptors."**

This mechanism of action (MOA) has been elevated to dogma because no agent has been approved for treating psychosis that does not exert a dopamine D2 receptor antagonist effect. However, as advances in the neurobiology of psychosis accelerate, several other functions of APs have been identified, which can be considered additional MOAs that may help mitigate psychosis' deleterious effect on brain tissue.

Consider the following beneficial effects of APs (especially second-generation APs [SGAs]) of which many clinicians are unaware:

APs suppress induction of pro-inflammatory cytokines.[1] It is well established that psychotic episodes of schizophrenia are associated with neuroinflammation and elevations of cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor (TNF-α), and interferon gamma (IFN-γ). These inflammatory biomarkers are released by microglia, which are rapidly activated by psychosis[2] and mediate brain tissue damage during psychosis. APs' rapid inhibitory action on pro-inflammatory cytokines obviously is neuroprotective.

APs suppress immune-inflammatory pathways.[3] This occurs with atypical agents but not haloperidol[4] and results in decreased IL-1β and IL-6 and transforming growth factor-β.

APs significantly decrease levels of neurotoxic tryptophan catabolites (TRYCATS) such as 3-OHK and QUIN, which mediate the immune-inflammatory effects on neuronal activity. APs also increase levels of neuroprotective TRYCATS such as kynurenic acid.[5]

APs activate cholesterol-transport proteins such as apolipoprotein E (APOE).[6] This implies that APs may improve low levels of APOE observed during psychosis and decrease myelination abnormalities and mitigate impairment of synaptic plasticity.[7,8]

APs increase neurotrophic growth factors that plummet during psychosis, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor.[9] This beneficial effect is seen with SGAs but not first-generation APs (FGAs) and is attributed to strong serotonin 5HT-2A receptor antagonism by SGAs.[10]

SGAs but not FGAs significantly increase the number of newly divided cells in the subventricular zone by 200% to 300%. This enhancement of neurogenesis and increased production of progenitor cells that differentiate into neurons and glia may help regenerate brain tissue lost during psychotic episodes.

Various SGAs have neuroprotective effects:

- Clozapine has neuroprotective effects against liposaccharide-induced neurodegeneration and reduces microglial activation by limiting production of

**Antipsychotics exert anti-immuno-inflammatory, antioxidative, and neuroplasticity effects**

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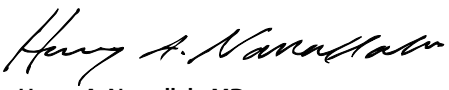
reactive oxygen species (free radicals).[11]

- Aripiprazole inhibits glutamate-induced neurotoxicity and, in contrast to haloperidol, increases BDNF, glycogen synthase kinase (GSK)-β, and the anti-apoptotic protein Bcl-2.
- Olanzapine increases BDNF, GSK-3β, and β-catenin, increases mitosis in neuronal cell culture, and protects against neuronal death in cell cultures that lack nutrients (which fluphenazine or risperidone do not).
- Paliperidone demonstrates a higher antioxidant effect than any other SGA and clearly is better than haloperidol, olanzapine, or risperidone in preventing neuronal death when exposed to hydrogen peroxide.
- Quetiapine, ziprasidone, and lurasidone have inhibitory effects on nitric oxide release. Quetiapine, but not ziprasidone, inhibits TNF-α.
- Ziprasidone inhibits apoptosis and microglial activation and synthesis of nitric oxide and other free radicals.
- Lurasidone increases BDNF expression in the prefrontal cortex of rodents.[13]

Although most clinicians uphold the dopamine neurotransmitter model of schizophrenia (ie, a hyperdopaminergic state that requires treatment with dopamine antagonists), research is moving toward a multi-faceted neurotoxicity and neuroprogression model of impaired neuroplasticity, neuroinflammation, immune dysfunction, oxidative stress, nitrosative stress, apoptosis, and mitochondrial dysfunction.[12] This complex model is shaping not only etiopathological research in schizophrenia but also its future management, including treatment of negative symptoms and cognitive deficits, not just delusions and hallucinations. Interestingly, the only treatment superior to placebo in preventing conversion to psychosis in ultra high-risk prodrome patients is omega-3 fatty acid, a strong anti-inflammatory agent,[14] which suggests that neuroinflammation may precede dopamine overactivity associated with the first psychotic episode.

Future treatments of schizophrenia, mania, and depression may focus on more aggressively diminishing inflammation and oxidative/nitrosative stress, not just modulating dopamine or other neurotransmitters, because progressive major psychiatric disorders have been associated with destructive neuroinflammation and an abundance of reactive oxygen species



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