Nicotine and Schizophrenia

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Nicotine is an alkaloid found in tobacco. It has long been known that use of tobacco, mainly in the form of cigarettes, is much more prevalent among patients with depression and schizophrenia. From the perspective of both healthcare providers and patients, this is often one of the most difficult aspects of psychiatric hospitalization. It is standard policy in most hospitals to forbid smoking on inpatient units, a situation that adds to the discomfort of patients admitted to psychiatric hospitals. By being forced to quit smoking, not only do they experience nicotine withdrawal, but, emerging evidence suggests, their psychiatric symptoms may get worse and they may become more prone to agitation. As a result, nicotine withdrawal can increase aggressive behavior.

An abstract presented at the 162nd Annual Meeting of the American Psychiatric Association in San Francisco, California, reported that, according to a randomized controlled trial, nicotine-replacement therapy decreased agitation and aggressive behavior in hospitalized patients with schizophrenia who smoke. According to Michael Allen, MD, the principal investigator, the nicotine patches were comparable to parenteral antipsychotics in reducing agitation. In the study, 40 smokers with schizophrenia were admitted to a psychiatric emergency unit and were screened at baseline for agitation. Patients were administered a 21-mg/day transdermal nicotine patch or placebo patch. At baseline, the agitation scores was significantly higher in the treatment group than the placebo group. During the 24-hour trial, patients who had gone without treatment or had inadequate treatment received 5 or 10 mg of intramuscular olanzapine or 5 mg of intramuscular haloperidol.

In a recent study using mice, researchers injected amounts of nicotine equivalent to what heavy smokers would consume. The findings suggested that there is a specific pathway by which nicotine increases γ-aminobutyric acid (GABA) synthesis. Nicotine bound to nicotine receptors on neurons in the frontal cortex and hippocampus of the brain. After binding to these receptors, nicotine dramatically down-regulated the production of an enzyme called deoxyribonucleic acid methyltransferase 1 (DNMT1). The loss or reduction of DNMT1 allowed brain cells to make more GABA. When nicotine was prevented from binding to the nicotinic receptor, DNMT1 could not be decreased and GABA levels could not be raised.

There are multiple alpha nicotinic receptors, but the α7 nicotinic acetylcholine receptor gene, CHRNA7, has been the focus of attention because of evidence that it is associated with genetic transmission of schizophrenia and related cognitive and neurophysiologic sensory gating deficits. This is of particular clinical importance because cognitive dysfunction produces much of the psychosocial disability among schizophrenic patients. Nicotine acts as a low-potency agonist at the α7 receptor, and emerging evidence shows that it has some positive effects on both the neurophysiologic and neurocognitive deficits associated with schizophrenia; this suggests that more effective receptor activation might meaningfully enhance cognition in schizophrenia. The investigators used 3-[(2,4-dimethoxy)benzylidene]anabaseine (DMXB-A), a natural alkaloid derivative and a partial α7 nicotinic cholinergic agonist, to determine if it could improve neurocognition as well as to assess, by effects on P50 auditory evoked potential inhibition, whether its neurobiologic actions are consistent with activation of α7 nicotinic receptors. The study
involved 12 patients with schizophrenia who were not cigarette smokers and were concurrently treated with antipsychotics. One person was withdrawn because of a transient decrease in white blood cell count. Administration of DMXB-A was found to result in significant neurocognitive improvement and significant improvement in P50 inhibition. Olincy and colleagues concluded that nicotinic agonists appear to have positive effects on neurocognition in people with schizophrenia.

In addition to schizophrenia, nicotinic receptor ligands are being studied as candidates for multiple central nervous system disorders including Alzheimer’s disease, attention-deficit/hyperactivity disorder, depression, pain, and addiction. 

REFERENCES

1. Allen M. Nicotine patches reduce agitation in smokers with schizophrenia. Abstract presented at the 162nd Annual Meeting of the American Psychiatric Association; May 18, 2009; San Francisco, California.