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Letter to the Editor

Can *N*-acetylcysteine, varenicline, or the combination prevent psychosis by enhancing mismatch negativity?

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Psychosis prevention

Dear Editor,

Preventing or delaying the onset of psychosis is an important area of research in the field of schizophrenia. There is substantial evidence that in people with clinical high risk (CHR) for psychosis, attenuated mismatch negativity (MMN) predicts conversion to first-episode psychosis (Bodatsch et al., 2011). The objective of this article is to highlight the role of *N*-acetylcysteine (NAC), varenicline, and the varenicline-NAC combination in preventing or delaying the conversion of CHR to psychosis.

NAC is US Food and Drug Administration (FDA) approved for the treatment of acetaminophen overdose and for use as a mucolytic (package insert). NAC is available over the counter. NAC has neuroprotective action by modulating oxidative stress, neuroinflammation, and glutamatergic systems. Varenicline, a partial agonist at the alpha-7 nicotinic acetylcholine (α7nACh) receptor, is an FDA-approved medication for smoking cessation (package insert).

In a randomized controlled trial (RCT) in schizophrenia, NAC significantly increased MMN compared to placebo (Lavoie et al., 2008). The authors argued that the MMN enhancement was the action of NAC on the *N*-methyl-D-aspartate (NMDA) receptors. In another RCT in early psychosis, NAC significantly improved auditory evoked potential (low-level auditory processing) compared to placebo (Retsa et al., 2018). In fact, NAC was proposed as a potential medication to prevent conversion to schizophrenia in individuals with CHR (Asevedo et al., 2012). However, the mechanism of action proposed was oxidative stress, inflammation, and glutamatergic system (see Fig. 1 in Asevedo et al., 2012). There are no available data on varenicline and MMN. However, encenicline, an α7 nicotinic partial agonist, enhanced MMN in individuals with schizophrenia (Preskorn et al., 2014). Thus, varenicline, which has a similar mechanism of action, may enhance MMN and prevent or delay psychosis onset. The underlying pathophysiological mechanism of MMN is nicotinic and NMDA receptors. In addition, the potential of the interactive effects of nicotinic acetylcholine and NMDA receptors on MMN is well documented (Knott et al., 2012; Hamilton et al., 2018). Because of the synergistic action of nicotinic and NMDA receptors, the galantamine-memantine combination may enhance MMN, thereby preventing psychosis onset (Koola, 2018). Similarly, the varenicline-NAC combination may enhance MMN more than either medication alone.

The neurodevelopmental hypothesis of psychosis suggests that disrupted white matter maturation underlies disease onset (Krakauer et al., 2018). There is growing evidence of abnormalities in the white matter integrity in people with CHR (Vijayakumar et al., 2016) and during the disease onset (Kochunov and Hong, 2014). In line with this evidence, in an RCT, NAC improved the fornix white matter integrity in early psychosis compared to placebo (Klauser et al., 2018). These findings could be translated to people with CHR. Hence, NAC can not only enhance MMN (Lavoie et al., 2008) but also protect the white matter integrity, which is an added advantage to prevent or delay psychosis onset.

The kynurenine pathway metabolites play an important role in brain development. Kynurenic acid (KYNA) is an antagonist of the α7nACh and NMDA receptors. Nicotinic and NMDA receptors are critically involved during neurodevelopment. The galantamine-memantine combination via α7nACh and NMDA receptors may counteract the effects of KYNA (Koola, 2018). Furthermore, it has been argued that "MMN and KYNA can be nipped in the bud" in CHR with the galantamine-memantine combination via action on the nicotinic and NMDA receptors (Koola, 2018). Similarly, the NAC-varenicline combination may also enhance MMN and counteract the effects of KYNA due to similar action on the NMDA and nicotinic receptors. For all these reasons, the NAC-varenicline combination may be considered a "me too" medication along with the galantamine-memantine combination to prevent or delay psychosis onset.

Substance use is common in individuals with CHR. In a meta-analysis, a significant association between current cannabis use disorder and transition to psychosis was found in individuals with CHR (Kraan et al., 2016). NAC may be efficacious for promoting abstinence from cocaine, tobacco, and cannabis (McClure et al., 2014). In a meta-analysis, NAC was found to be superior to placebo for craving reduction (Duailibi et al., 2017). Hence, NAC may be beneficial not only for preventing psychosis onset by enhancing MMN but also for reducing substance use. Similarly, varenicline is likely to reduce tobacco use and enhance MMN to prevent psychosis onset.

With no approved treatments available to prevent psychosis onset, RCTs with NAC, varenicline, and the combination are needed to shed light on whether these medications can prevent or delay CHR to psychosis with MMN enhancement as a biomarker.

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Conflict of interest

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Contributors

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References

Asevedo, E., Cunha, G.R., Zugman, A., Mansur, R.B., Brietzke, E., 2012. *N*-acetylcysteine as a potentially useful medication to prevent conversion to schizophrenia in at-risk individuals. Rev. Neurosci. 23 (4), 353–362.

Bodatsch, M., Ruhrmann, S., Wagner, M., Müller, R., Schultze-Lutter, F., Frommann, I., Brinkmeyer, J., Gaebel, W., Maier, W., Klosterkötter, J., Brockhaus-Dumke, A., 2011. Prediction of psychosis by mismatch negativity. Biol. Psychiatry 69 (10), 959–966.

Duailibi, M.S., Cordeiro, Q., Brietzke, E., Ribeiro, M., LaRowe, S., Berk, M., Trevizol, A.P., 2017. *N*-acetylcysteine in the treatment of craving in substance use disorders: systematic review and meta-analysis. Am. J. Addict. 26 (7), 660–666.

Hamilton, H.K., D'Souza, D.C., Ford, J.M., Roach, B.J., Kort, N.S., Ahn, K.H., Bhakta, S., Ranganathan, M., Mathalon, D.H., 2018. Interactive effects of an *N*-methyl-D-aspartate receptor antagonist and a nicotinic acetylcholine receptor agonist on mismatch negativity: implications for schizophrenia. Schizophr. Res. 191, 87–94.

Klauser, P., Xin, L., Fournier, M., Griffa, A., Cleusix, M., Jenni, R., Cuenod, M., Gruetter, R., Hagmann, P., Conus, P., Baumann, P.S., Do, K.Q., 2018. *N*-acetylcysteine add-on treatment leads to an improvement of fornix white matter integrity in early psychosis: a double-blind randomized placebo-controlled trial. Transl. Psychiatry 8 (1), 220.

Knott, V., Shah, D., Millar, A., McIntosh, J., Fisher, D., Blais, C., Ilivitsky, V., 2012. Nicotine, auditory sensory memory, and sustained attention in a human ketamine model of schizophrenia: moderating influence of a hallucinatory trait. Front. Pharmacol. 3, 172.

Kochunov, P., Hong, L.E., 2014. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. Schizophr. Bull. 40 (4), 721–728.

Koola, M.M., 2018. Attenuated mismatch negativity in attenuated psychosis syndrome predicts psychosis: can galantamine-memantine combination prevent psychosis? Mol. Neuropsychiatr. 4, 71–74.

Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H.K., van den Berg, D., de Haan, L., van der Gaag, M., 2016. Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. Psychol. Med. 46 (4), 673–681.

Krakauer, K., Nordentoft, M., Glenthøj, B.Y., Raghava, J.M., Nordholm, D., Randers, L., Glenthøj, L.B., Ebdrup, B.H., Rostrup, E., 2018. White matter maturation during 12 months in individuals at ultra-high-risk for psychosis. Acta Psychiatr. Scand. 137 (1), 65–78.

Lavoie, S., Murray, M.M., Deppen, P., Knyazeva, M.G., Berk, M., Boulat, O., Bovet, P., Bush, A.I., Conus, P., Copolov, D., Fornari, E., Meuli, R., Solida, A., Vianin, P., Cuénod, M., Buclin, T., Do, K.Q., 2008. Glutathione precursor, *N*-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 33 (9), 2187–2199.

McClure, E.A., Gipson, C.D., Malcolm, R.J., Kalivas, P.W., Gray, K.M., 2014. Potential role of *N*-acetylcysteine in the management of substance use disorders. CNS Drugs 28 (2), 95–106.

Preskorn, S.H., Gawryl, M., Dgetluck, N., Palfreyman, M., Bauer, L.O., Hilt, D.C., 2014. Normalizing effects of EVP-6124, an α-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. J. Psychiatr. Pract. 20 (1), 12–24.

Retsa, C., Knebel, J.F., Geiser, E., Ferrari, C., Jenni, R., Fournier, M., Alameda, L., Baumann, P.S., Clarke, S., Conus, P., Do, K.Q., Murray, M.M., 2018. Treatment in early psychosis with *N*-acetyl-cysteine for 6months improves low-level auditory processing: pilot study. Schizophr. Res. 191, 80–86.

Vijayakumar, N., Bartholomeusz, C., Whitford, T., Hermens, D.F., Nelson, B., Rice, S., Whittle, S., Pantelis, C., McGorry, P., Schäfer, M.R., Amminger, G.P., 2016. White matter integrity in individuals at ultra-high risk for psychosis: a systematic review and discussion of the role of polyunsaturated fatty acids. BMC Psychiatry 16 (1), 287.

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