Media Release: European College of Neuropsychopharmacology (ECNP) Congress, Paris

"For the science and treatment of disorders of the brain"

Study shows contrasting long-term cognitive effects of psychiatric drugs in schizophrenia

For immediate release, Tuesday 5th September

PARIS, France: A long-term study has found that low cumulative exposure to benzodiazepine and antidepressant medications does not seem to affect cognition in schizophrenia. However, long-term high-dose use of antipsychotic drugs seemed to be associated with poorer cognition, whereas a relatively long break in antipsychotic use was associated with better cognitive functioning. This work, the first to follow lifetime exposure to benzodiazepines and antidepressant in schizophrenia, is presented at the ECNP conference in Paris, and it is also published in the peer-reviewed journal European Psychiatry*.

Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 21 million people worldwide **. It is most often a lifelong disorder, requiring long-term treatment and rehabilitation and long-term use of antipsychotic medication. However, drug trials are usually of short duration, for example antipsychotic trials last up to 2-3 years. As many medicines are used over long periods and may be linked with significant side-effects, it is important to be able to follow these effects in the long-term.

Now a group of researchers from the Universities of Oulu (Finland) and Cambridge (UK) is presenting observational data on the long-term use of psychiatric drugs in schizophrenia. The researchers followed participants from the Northern Finnish Birth Cohort 1966 – meaning that all the persons had been born in 1966. 60 of the participants had been diagnosed with a schizophrenia spectrum disorder, and had received different medications over the long-term. The individuals underwent an extensive series of cognitive tests when they were 43 years old, having had an average medicine use lasting 16.5 years.

The researchers found that modest long-term use of common psychiatric medications, benzodiazepines and antidepressants, had no noticeable effect on cognition. However, they contrast this with their previous finding (reported in January 2017, see below) that the high-dose use of antipsychotic drugs was associated with poorer cognition in the long-term, by reporting that long breaks in antipsychotic treatment seems to result in better cognitive functioning.

According to lead researcher, Anja Hulkko MD (University of Oulu):

"These are mixed results, which show different outcomes. Firstly, low long-term use of benzodiazepines and antidepressants doesn't seem to have adverse effects on cognition in patients with schizophrenia. These are not the primary medicine prescribed to people with schizophrenia to target psychotic symptoms. If there is little if any cognitive harm in using them with small doses or

for short periods of time, then they may be promoted for anxiety, depression, or sleeplessness, which can be undertreated. It should be noted that, high-dose long-term use of benzodiazepines has been associated with poorer cognition and according to treatment recommendations should be avoided.

However, this work reinforces the work we published earlier this year on long-term high-dose antipsychotic use, by showing that long breaks in antipsychotic treatment right before neuropsychological assessment may be associated with better cognitive functioning in schizophrenia. People with more severe illness are often prescribed higher doses of antipsychotics and those with milder illness may manage longer periods of time with smaller doses or even without antipsychotic treatment. It is important that patients continue to take antipsychotic medicines as prescribed, as discontinuing treatment can lead to severe consequences. However, it is also important that patients work with their doctors to find the minimum effective dose for the long-term, and perhaps consider psychosocial treatments and cognitive rehabilitation.

We should note that because of the observational setting of our study and small sample size, definitive conclusions are difficult to draw, even though in our analyses controlling for severity or duration of illness didn't explain the cognitive findings with antipsychotics. Owing to the extensive birth cohort database, we were able to control for many relevant variables. However, during a long illness course the risk of missing some important confounders increases – for example, more ill persons with more cognitive problems may also be given more medication. It seems likely that both the illness itself and treatment are associated with the course of cognition".

Commenting, Professor Kamilla Miskowiak, of Copenhagen University Hospital, Denmark (who was not involved in the study) said:

"This is a highly interesting study which shows no long-term cognitive side-effects of antidepressants, tranquilizers or low-dose antipsychotic medication in schizophrenia. This is reassuring since many patients are worried about taking these medications because of their potential negative effects on cognition. In contrast, long-term high-dose antipsychotic medication was associated with poorer cognitive outcome. This underscores the importance of close dose monitoring of antipsychotic medication for these patients to improve their cognitive outcome".

This is the first report of the association between lifetime cumulative benzodiazepine and antidepressant exposures and cognition in midlife schizophrenia. The authors note that this is a small sample and an observational study. This limits what can be said about the safety of these drugs. Long-term treatment outcomes should be in the focus of future studies.

*European Psychiatry 45 (2017) 50–58, September 2017
For background see: **Schizophrenia Prof Jim van Os, Prof Shitij Kapur, PhD http://www.thelancet.com/action/showFullTextImages?pii=S0140-6736%2809%2960995-8

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Notes for Editors

Please mention the ECNP Conference in any story resulting from this press release

The European College of Neuropsychopharmacology (ECNP)

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 30th annual ECNP Congress takes place from 2nd to 5th September in Paris. It is Europe's premier scientific meeting for disease-oriented brain research, annually attracting between 4,000 and 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: http://2017.ecnp.eu/

Conference Abstract: Lifetime use of psychiatric medications and cognition at 43 years of age in schizophrenia in the Northern Finland birth cohort 1966 A. Hulkko[1]*, G.K. Murray[2], J. Moilanen[1], M. Haapea[3], I. Rannikko[1], S. Huhtaniska[1], P.B. Jones[2], J.H. Barnett[2], M. Isohanni[4], H. Koponen[5], E. Jääskeläinen[3], J. Miettunen[3]

Background: Higher lifetime exposure to antipsychotic medication has been associated with poorer cognition in schizophrenia [1], [2]. The cognitive effects of adjunctive psychiatric medications, antipsychotic polypharmacy and lifetime trends in use of antipsychotics remain largely unclear.

Aims: To study how lifetime and current exposure to benzodiazepines and antidepressants, lifetime trends of and current antipsychotic use and antipsychotic polypharmacy are associated with global cognitive performance in midlife schizophrenia in a birth cohort sample.

Methods: Sixty participants with a schizophrenia spectrum disorder (DSM-IV) from the Northern Finland Birth Cohort 1966 (NFBC 1966) were examined after 16.5 years of illness at 43 years of age with an extensive cognitive test battery, including the Abstraction Inhibition and Working Memory task, California Verbal Learning Test, Visual Object Learning Test, Verbal fluency, Visual series, Vocabulary, Digit Span and Matrix reasoning. The psychiatric medications were classified based on the Anatomical Therapeutic Chemical (ATC) system to benzodiazepines (including benzodiazepine derivatives N05BA, N03AE and N05CF, and benzodiazepine related drugs N05CD), antidepressants (N06A) and antipsychotics (N05A). Cumulative lifetime Defined Daily Dose (DDD) years and cross-sectional doses (DDD-ratios) were collected from medical records and interviews. The associations between medication and principal component analysis-based cognitive composite score were analysed using linear regression.

Results: Lifetime cumulative DDD years and current DDD-ratios of benzodiazepines and antidepressants were not significantly associated with global cognition. Having an antipsychotic-free period of at least one year at any time since the start of treatment ($p=0.028$) or at least about 11 months before the cognitive examination ($p=0.007$) was associated with better global cognitive performance, when adjusted for gender, onset age and lifetime hospital treatment days and also when controlled for several other potential confounders. Proportion of long-term antipsychotic use or proportion of lifetime or current antipsychotic polypharmacy were not significantly associated with cognition.

Conclusions: To our knowledge, this is the first report of the association between lifetime cumulative benzodiazepine and antidepressant exposures and cognition in midlife schizophrenia. Based on these naturalistic data, adjunctive benzodiazepine and antidepressant medications do not seem to greatly affect cognition nor explain the cognitive effects of antipsychotic medication in schizophrenia. The association between better cognitive performance and having a relatively long break in antipsychotic medication at any time since the start of treatment may be explained by lower cumulative exposure to antipsychotics and thus is consistent with possible negative cognitive effects of long-term high-dose antipsychotic medication [1], [2]. In the NFCB 1966, both low lifetime antipsychotic dose and not having antipsychotic-free periods of ≥30 days associated with better functional outcome in schizophrenia [3]. The relationship between breaks in antipsychotic treatment and cognitive and functional outcomes in schizophrenia seems complex. Residual confounding related to the naturalistic design, may partly explain these results. Nevertheless, with the cumulating evidence of associations between high-dose, long-term antipsychotic exposure and change in volume of brain structures [4] and functioning [5], it is possible that high-dose antipsychotic medication may harm cognition in schizophrenia in the long-term.

Full attribution and references available on conference website

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How this was reviewed?

There were 1003 abstracts accepted for this conference, this work was amongst the top-scoring 170 abstracts. After initial approval from the ECNP media group, the press release was developed by the press officer and the author, with the final version being approved by the ECNP media review group. We then sought an additional view and comment from someone with expertise in the field – this is the person who comments in the press release. None of the reviewers have been involved in the work.