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Obsessive-compulsive Symptoms in Schizophrenia: Multimodal Prospective Investigations

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Several causal explanations have been proposed for the high prevalence of obsessive-compulsive symptoms (OCS) in patients with schizophrenia. Within the range of possible pathomechanisms the hypothesis arose that second generation antipsychotics (SGAs) with pronounced antiserotonergic pharmacodynamic properties, in particular clozapine, might induce OCS as a side effect.

Patients with schizophrenia in SGA monotherapy were prospectively investigated over a period of 12 months. The multimodal approach included the assessment of pharmacotherapy, psychopathology, neuropsychology and neurogenetics. Within the heterogeneous clinical presentation of OCS in schizophrenia, results significantly contribute to relevant concepts regarding the neurobiological basis, the course of comorbid OCS during SGA treatment and implications for treatment approaches.

Study 1 & 2: For the longitudinal investigation of possible differential pharmacological effects on the development and course of comorbid OCS, schizophrenia patients were classified into two groups according to their antipsychotic monotherapy before baseline assessment. Participants treated with potent serotonergic antagonists combined with rather weak antidopaminergic effects such as clozapine (CLZ) and olanzapine (OLZ) formed group I, while predominantly dopaminergic SGAs such as amisulpride (AMS) and aripiprazole (APZ) were classified as group II.

In the first cross-sectional evaluation of a subsample of 70 individuals onset, prevalence and severity of OCS were compared in relation to SGA treatment: Patients treated with CLZ or OLZ suffered more frequently and more severely from OCS than patients under AMS or APZ treatment and significant correlations between OCS severity and dosage as well as duration of index treatment were found within group I.

An enlarged sample of 75 individuals was followed-up over a 12-month period with the primary endpoint of group-specific, intra-individual changes in OCS severity over time. Group I showed markedly higher YBOCS scores at both time points. Repeated measure analyses

of variance revealed significant interaction effects of group and time. This was due to persistently high OCS severity within group I, and decreasing YBOCS-scores within group II. The observed differential course of OCS in the two groups hints towards on-going pro-obsessive effects of antiserotonergic SGAs within group I, and provides preliminary findings, which support favourable effects of APZ and AMS on comorbid OCS within group II. Results thereby support the concern that treatment with antiserotonergic antipsychotics might be associated with the risk of inducing or aggravating OCS in schizophrenia.

Study 3: A recent genetic association study in an Asian sample reported associations between SGA-induced OCS and polymorphisms in the gene *SLC1A1* encoding the neuronal glutamate transporter EAAC1 (excitatory amino acid carrier). To replicate this finding, an extended sample of 103 patients with schizophrenia who were of European descent was examined. Three single-nucleotide polymorphisms in *SLC1A1* (rs2228622, rs3780412 and rs3780413) were investigated. In contrast to the Asian sample, neither single marker, nor haplotype analyses found associations with OCS. Consequently, larger samples are necessary to untangle the interplay of pharmacological and genetic risk factors for OCS in schizophrenia.

Study 4: To investigate the association between comorbid OCS and cognitive impairment, the classification of 80 participants was revised and presence or absence of comorbid OCS determined the groups. Performance in a comprehensive cognitive test-battery was compared between groups at baseline and again 12 months later. Schizophrenia patients with OCS showed pronounced deficits with increasing effect sizes over time in specific cognitive areas such as visuo-spatial perception and visual memory, executive functioning and cognitive flexibility, when compared to schizophrenia patients without OCS. These cognitive domains correlated with OCS severity and are known to be candidate domains in obsessive-compulsive disorder (OCD).

In conclusion, the present prospective, multimodal investigations suggest that a significant subgroup of patients with schizophrenia develops comorbid OCS as a consequence of their antipsychotic medication with pronounced antiserotonergic properties and that these symptoms will persist or even be aggravated under ongoing treatment. OCS in schizophrenia was further associated with specific and longitudinally stable cognitive deficits. Longitudinal studies involving patients in the early stages of psychotic illness are necessary to decipher the interaction of affective, psychotic and obsessive-compulsive syndromes and their partially overlapping neurobiological correlates. From a therapeutic viewpoint, results emphasize the need for the definition of risk factors and the early detection and monitoring of OCS. Forthcoming treatment trials should focus on possible pharmacological interventions and cognitive behavioural therapy for patients with schizophrenia suffering from comorbid OCS.