OBSESSIVE-COMPULSIVE DISORDERS: PT609 – PT625

PT609

A rapid improvement in obsessive-compulsive disorder with milnacipran in a schizophrenic patient

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Abstract

A substantial portion of schizophrenia patients with obsessive compulsive disorder fail to respond to regimen of antipsychotic and selective serotonin reuptake inhibitor. Herein, we report a schizophrenic patient who, after being switched from escitalopram to milnacipran, showed a rapid improvement of his debilitating OCD.

A 23-year-old unemployed single man had been diagnosed with schizophrenia and OCD 4 years previously. A regimen with quetiapine 225 mg/day and escitalopram 20 mg/day has stabilized his psychotic symptoms, however, OCS persisted, with a score of 24 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). We switched escitalopram to milnacipran at an initial dosage of 100 mg/day, without adding on any psychological or behavioral interventions. By the end of the first week after initiating milnacipran, his Y-BOCS score had dropped to 13. The dose of milnacipran was raised to 150 mg/day at the third week, the patient showed a reduction of about 45% in Y-BOCS score, which is considered to be a significant treatment response.

Milnacipran is a unique SNRI in that it is twice as potent in inhibiting norepinephrine than serotonin reuptake. Among schizophrenic patients, the serotonergic system may receive complex dopaminergic modulations which are further complicated with antipsychotic treatment. In the present case, it is possible that a paradoxical downregulation of serotonergic receptors following his previous antipsychotic treatment may have hindered the therapeutic efficacy of SSRIs in treating OCS. SNRIs with preferential norepinephrine reuptake inhibition, such as milnacipran, may exert a superior efficacy by acting primarily on the noradrenergic circuit. Due to the complex interplay between serotonergic, dopaminergic and noradrenergic systems, the pathogenesis of OCS in patients with schizophrenia may be more complicated than the well-known serotonin hypothesis of OCD. Milnacipran, with its preferable noradrenergic reuptake blockade, can be a reasonable alternative if OCS fail to respond to SSRIs or other SNRIs.

PT610

Aripriprazole augmentation in patient with OCD partially responsive to SSRI

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Abstract

Objective: Despite the efficacy of SSRIs and clomipramine, 40%-60% of patients with obsessive-compulsive disorder do not respond adequately to the first line of treatment. This was the case of our patient, a 34-year old female, who demonstrated pronounced magical thinking and an obsessive fear that something terrible would happen to family members. She sought to reduce the impact of these thoughts with mental and motor compulsions (counting, repeating thoughts, bringing things into order and symmetry). Obsessive thoughts and compulsions took up several hours a day, making her exhausted, depressed and inefficient.

Aims: As the previous treatment with an SSRI (paroxetine) after 3 months at the maximum tolerated dose (40mg/day) gave only a partial therapeutic response, we augmented the treatment with aripriprazole at a dose of 5mg/day. Review of the literature indicates that adding aripiprazole to an SSRIs could be a valid strategy for treatment-resistant OCD patients or those with only a partial therapeutic response. Aripiprazole is associated with a lower risk of weight gain, sedation, and increase in prolactin compared to other antipsychotics.

Method: The following instruments were applied before and two weeks after aripriprazole augmentation: The Beck Anxiety Inventory (BAI), the Beck Depression Inventory-II (BDI-II) and the Obsessive-Compulsive Inventory-Revised (OCI-R). We also followed patients for possible side-effects.

Results: Scores on the applied instruments were as follows: before the augmentation with aripriprazole: BAI=10; BDI-II=28, OCI-R= 21; after augmentation with aripriprazole: BAI =3, BDI-II =10, OCI-R=8.

Conclusions: Aripriprazole augmentation in a dose of 5mg/day was effective in reduction of obsessive-compulsive symptoms in a patient with partial therapeutic response to paroxetine, as well as in generalized anxiety and depression, with rapid onset of improvement (after 2 weeks of initiation) and good tolerability.

References

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PT611

The combination of sub-effective doses of agmatine and ketamine reduces obsessive-compulsive-like behavior of mice in marble burying test

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Abstract

Objective: Obsessive compulsive disorder (OCD) is a debilitating psychiatric disorder still having lack of effective treatment of which the pathophysiology has been linked to glutamatergic dysfunction. Ketamine, having rapid antidepressant effect, was shown to reduce OCD symptoms supporting the glutamatergic perspective (1,2). Agmatine, an imidazoline and alpha adrenergic binding agent is an N-methyl-D-aspartate (NMDA) receptor antagonist and nitric oxide sythase inhibitor. It has recently been shown to reduce compulsive-like behaviors of mice in the marble burying (MB) test at a dose of 20 mg/kg but not 10 mg/kg (3). Herein, we examined possible potantialization of ketamine and agmatine in anticompulsive-like effect in marble burying test.

Methods: Balb/c mice in both sexes (25–40 g) were divided into Control (saline), Ketamine (3 mg/kg), Agmatine (10 mg/kg), Ketamine+Agmatine (3 mg/kg+10 mg/kg) groups (n=10–20 in

each). MB test was applied 30 min after i.p. drug administrations. In the marble burying test, 20 glass marbles, each about 4 cm apart, are arrayed on the surface of 5 cm thick sawdust bedding. The number of marbles buried (to 2/3 their depth) in a 30 min session were counted. Open field test was also conducted for locomotor activity. One-way analysis of variance (ANOVA) was used for statistical analysis followed by Tukey's test.

Results: The number of marbles buried was not significantly different in agmatine ($p>0.05$) or ketamine ($p>0.05$) alone groups compared to control. When combined together in the same dosage regimen, the number of marbles buried was statistically less than control group ($p<0.05$).

Conclusions: When administered alone at sub-effective doses, neither ketamine nor agmatine reduced compulsive-like behaviors. However, the combination of them resulted in potantialization in anticompulsive-like effects. It could be of interest to identify shared or distinct mechanisms of these molecules possibly responsible for the proposed behavioral manifestation seen in this compulsive model.

Key words: marble burying, ketamine, agmatine

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PT612

Common variants of 5-HT3 receptor genes are associated with obsessive-compulsive disorder and its phenotypic expression

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Abstract

Objective: Evidence in the extant literature has indicated associations between serotonin-related genetic variants and obsessive-compulsive disorder (OCD), but few studies have explored the involvement of serotonin receptor type 3 genes in OCD. The present study aimed to identify whether *HTR3* genetic variants may affect susceptibility to OCD.

Methods: Ten common *HTR3* variants were examined in 596 individuals with OCD and 599 controls. Single-marker association and haplotype-based association analyses were conducted regarding the affected status and different OCD sub-phenotypes, such as age at onset and clinical symptom dimensions. The impact of *HTR3* variants on trait disgust sensitivity was also analyzed.

Results: A significant difference in the genotype distribution of rs1176744 was detected between individuals with OCD and controls (odds ratio (OR) = 0.74, 95% confidence intervals (CI) = 0.60–0.91, p = 0.0044). A two-marker composite haplotype in *HTR3B* was also associated with OCD (OR = 0.77, CI = 0.63–0.95, permutated p = 0.0185). On analyzing clinical characteristics of OCD, significant associations were found for rs3758987 with age at onset in male subjects (OR = 0.49, CI = 0.30–0.78, p = 0.0025) and for rs6766410 and rs6443930 with the contamination/cleaning dimension in female subjects (OR = 0.36, CI = 0.18–0.69, p = 0.0017 and OR = 0.47, CI = 0.29–0.78, p = 0.0029, respectively). In addition, rs6766410 was significantly related to contamination-based disgust scores in the whole OCD sample (p = 0.0045).

Conclusions: Our results support a role for common variants of *HTR3* in OCD and certain of its clinical phenotypes. These findings may have implications for pharmacogenetic studies of 5-HT_3 antagonists in the treatment of OCD.

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The Role of SKA2 Genetic and Epigenetic Variation in Obsessive-Compulsive Disorder

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Abstract

Background: OCD has a strong genetic component, is highly comorbid with MDD, and is often triggered by stress. Genetic and epigenetic variation in *SKA2* has been implicated in mediating stress response, and has recently been associated with suicidal behavior in MDD (Kaminsky, 2014). The *SKA2* polymorphism rs7208505 exhibits allele-specific methylation. We hypothesized that genetic and epigenetic variation at *SKA2* may play a role in OCD disease risk and severity.

Methods: A sample of n=64 OCD patients, divided equally by presence/absence of comorbid MDD, and age and gender matched, were selected. Y-BOCS score was used to measure disease severity. Genotypes for rs7208505 were compared to Caucasian controls (n=379, 1000 Genomes Project) using Fisher's Exact test. The relationship among the rs7208505 variant, OCD disease severity, and MDD status was analyzed using ANCOVA. DNA methylation levels were quantified using bisulfite pyrosequencing. Pearson's r was used to investigate the correlation between percentage methylation and OCD symptom severity.

Results: The *SKA2* rs7208505 genotypes significantly differed between OCD patients and controls (χ^2=10.21, p=0.006). The CC genotype was significantly associated with lower symptom severity than the CT/TT genotypes (F(3,52)=4.709, p=0.006). Percent methylation was negatively correlated with OCD severity (r=-0.438, n=56, p=0.001). Neither genetic nor epigenetic variation of rs7208505 was associated with comorbid MDD status.

Conclusions: These results provide some evidence that *SKA2* genetic and epigenetic variation may be a predictor of OCD risk and severity, regardless of MDD comorbidity; however, replication in larger samples is required. Further work will include interrogating additional genetic and epigenetic variations in *SKA2*.