CLOZAPINE AND WEIGHT GAIN - ASSOCIATION WITH CLINICAL RESPONSE AND LONG-TERM COURSE

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Weight gain during short-term clozapine treatment is well known. It has been reported to correlate with treatment response. The long-term course of weight gain during clozapine treatment has not been well studied. In a sample of 73 mostly schizophrenic patients, we investigated weight change during short- and long-term treatment (up to 90 months) with clozapine and its correlation with treatment response. The patients showed significant weight increase during the first 12 weeks, reaching a significant weight gain by the second week. Responders and non-responders by week 6 or 12, respectively, did not differ in regard to weight gain by those respective weeks. Also, weight gain during the first 8 weeks was not particularly correlated with treatment response after 6 months. Survival analysis revealed that 80% of the patients gained at least 10% weight and about a third of the patients showed an increase of 20% or more. More than half the patients became overweight by 20% or more. The results indicate that weight gain during clozapine treatment is a significant clinical problem with potentially adverse effects to patients. Research into its treatment is needed.

THE FUNCTIONAL SIGNIFICANCE OF SYMPTOMATOLOGY AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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Schizophrenia is characterized by three general categories of impairment: (1) positive symptoms (2) negative symptoms and (3) cognitive deficits. In addition, adaptive functioning--an individual's ability to perform basic activities of daily living (ADL's) such as grooming, cooking, and cleaning--is often severely compromised in patients with this illness. While recent studies have addressed the relationships between symptomatology and cognitive dysfunction in schizophrenia, studies which have examined these variables in relation to adaptive functioning have tended to focus on global indices of functional ability, such as social and occupational functioning. There is little information regarding the relationship between symptomatology, cognitive impairment and adaptive functioning in terms of specific ADL's. Ability to perform ADL's is an important treatment outcome variable which has often been overlooked. For the present study, subjects were 110 patients meeting DSM III-R criteria for schizophrenia or schizoaffective disorder who were recently hospitalized for an acute exacerbation of illness. Measures of positive symptoms (Brief Psychiatric Rating Scale), negative symptoms (Negative Symptom Assessment (NSA)), and adaptive functioning (Functional Needs Assessment (FNA)) were obtained following 2 weeks of treatment with standard antipsychotic medications. Multiple regression analyses were used to examine the relative utility of positive versus negative symptomatology in predicting concurrent adaptive functioning. Results revealed that negative symptoms (global NSA score) predicted almost 30% of the variance in FNA scores. Positive symptoms did not explain additional variance. When the 6 factors composing the NSA were utilized as independent variables predicting to FNA scores, results revealed that the "cognition" factor was the only factor predicting functional ability, accounting for 46% of the variance in FNA scores. As new drug treatments are developed which allow more patients to be discharged, it will be increasingly important to be able to predict functioning outside the hospital. The NSA "cognition" factor may be a simple, cost effective way to do this. In addition, treatments which help compensate for the cognitive deficits underlying functional impairments should be pursued.

NMDA receptors mediate diffuse homolateral cerebrocortical changes in gene expression following a minimal cortical lesion.

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A small surgical lesion of the parietal cortex induces an increase in gene expression varying from 172 to 980% in the entire homolateral cerebral cortex, as detected by quantitative in situ hybridization histochemistry. The mRNAs encoding the immediate early genes of the leucine zipper family (c-fos, c-jun, jun-B), the zinc finger family (zif268), the glucocorticoid receptor family (NGF1-B) and the interferon family (PC4) are increased within two hours after the lesion and return to normal levels at six hours. The mRNAs encoding neuropeptides cholecystokinin, neuropeptide Y, somatostatin and the synthetizing enzyme of the neurotransmitter gamma amino butyric acid, glutamic acid decarboxylase, are elevated within one day and return to normal levels after six days. The increase in CCK neuropeptide is followed by a decrease in the number of CCK binding sites 3 days after lesion, as measured by autoradiography using CCK-8 (sulphated) I125-labelled with Bolton & Hunter reagent. An intraperitoneal injection of the NMDA receptor antagonist MK801, 30 min before surgery, prevented both the induction of immediate early gene expression and the increase of neuropeptide and glutamic acid decarboxylase mRNAs expression. This study demonstrates that a minimal cortical lesion induces extensive changes in gene expression and that some of the mechanism(s) leading to these changes involves the glutamate NMDA receptor.

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EFFECTS OF NEFAZODONE ON SLEEP ARCHITECTURE AND DAYTIME ALERTNESS

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Nefazodone is a new antidepressant drug that is both a 5-HT_2 antagonist and a serotonin reuptake inhibitor. It has been demonstrated to be safe and effective for the treatment of patients with major depression.

This double-blind, randomized, parallel group study compared the effects of nefazodone and placebo on sleep architecture and daytime alertness in 22 normal volunteers. Polysomnographic recordings were obtained in the sleep laboratory for each subject (11 per treatment group) during a 3-night placebo run-in period, 8 nights of a 2-week treatment period, and 2 nights of placebo washout. Nightly time in bed was controlled at 480 minutes for all subjects. Following the single-blind placebo run-in period, subjects were randomized to receive either nefazodone or placebo. Nefazodone was dosed at 100 mg BID during the first treatment week and 200 mg BID during the second week. Daytime alertness was evaluated using the Multiple Sleep Latency Test (MSLT) before, during, and after treatment.

Compared with placebo, nefazodone did not disrupt normal sleep architecture and, unlike most other antidepressant drugs, it had no effect on REM sleep (time, density, or latency). Although nefazodone is mildly sedating clinically, it had no overall effect on total sleep time (or sleep efficiency) or the number of awakenings. In addition, all other aspects of sleep architecture, including the proportion of slow wave (stage 3 and 4) sleep, were unchanged after two weeks of treatment. The MSLT showed no evidence that nefazodone caused daytime sleepiness.