



Pakistan Journal of Neurological Sciences (PJNS)

Volume 2 | Issue 1

Article 9

4-2007

Psychiatry

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Recommended Citation

Ahmer, Syed (2007) "Psychiatry," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 2 : Iss. 1 , Article 9.
Available at: <https://ecommons.aku.edu/pjns/vol2/iss1/9>

PSYCHIATRY

COMMENTARY

Is addiction an illness or simply bad behavior? Do addicts have a biological predisposition to become addicts or do they only have themselves to blame? These questions have been debated by psychiatrists for most of the last century and have had a major influence on how professionals approach treatment of drug addiction. Now Boileau et al show that on repeated exposure to amphetamine the human brain becomes sensitized to it and releases relatively more dopamine on subsequent administration of the substance with the effects lasting upto a year, suggesting that there may be a biological substrate to addiction.

The discovery of atypical antipsychotics with decreased likelihood of causing extrapyramidal side effects at therapeutic doses was heralded as a paradigm shift in the treatment of schizophrenia. But it soon became apparent that these drugs had problems of their own with excessive weight gain, dyslipidemia, impaired glucose tolerance and type 2 diabetes mellitus topping the list. Klein et al now show that concomitant use of metformin is safe and efficacious in abrogating weight gain, decreased insulin sensitivity, and abnormal glucose metabolism in children and adolescents taking atypical antipsychotics.

The tradition of dividing illnesses into 'organic' and 'functional' has been a long one in psychiatry, somehow implying that psychiatric illnesses were diseases of the 'mind' and not of the 'brain'. Many studies in the last quarter of a century have shown that there were detectable abnormalities in the brain in patients with schizophrenia compared with normal controls. Jayakumar et al add further weight to that evidence by demonstrating volumetric and metabolic abnormalities in caudate nuclei of antipsychotic-naïve patients with schizophrenia compared with normal controls.

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Archives of General Psychiatry 2006 Dec; 63:1386-1395.

Boileau I, Dagher A, Leyton M, Gunn RN, Baker GB, Diksic M, Benkelfat C.

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MODELING SENSITIZATION TO STIMULANTS IN HUMANS: AN [11C]RACLOPRIDE/POSITRON EMISSION TOMOGRAPHY STUDY IN HEALTHY MEN

CONTEXT: In animals, repeated exposure to stimulant drugs leads to an enhanced drug-induced psychomotor response and increased dopamine release. This phenomenon, known as sensitization, may confer vulnerability to drug addiction or drug-induced psychosis in humans. A similar phenomenon, referred to as endogenous sensitization, is also believed to play a role in the emergence of positive symptoms in patients with schizophrenia. **OBJECTIVE:** To determine whether behavioral and neurochemical sensitization occur in healthy individuals after limited exposure to amphetamine in the laboratory. **DESIGN:** Open-label, 1-year follow-up of repeated amphetamine administration in healthy volunteers. **SETTING:** Department of Psychiatry, McGill University, and McConnell Brain Imaging Center, Montreal Neurological Institute. **PARTICIPANTS:** Ten healthy men (mean +/- SD age, 25.8 +/-

1.8 years). **INTERVENTION:** Three single doses of amphetamine (dextroamphetamine sulfate, 0.3 mg/kg by mouth) were administered on days 1, 3, and 5. **MAIN OUTCOME MEASURES:** Using positron emission tomography and [11C]raclopride, we measured dopamine release in response to amphetamine on the first exposure (day 1) and 14 days and 1 year after the third exposure. **RESULTS:** The initial dose of amphetamine caused dopamine release in the ventral striatum (a reduction in [11C]raclopride binding). Consistent with a sensitization-like phenomenon, 14 and 365 days after the third dose of amphetamine there was a greater psychomotor response and increased dopamine release (a greater reduction in [11C]raclopride binding), relative to the initial dose, in the ventral striatum, progressively extending to the dorsal caudate and putamen. A high novelty-seeking

personality trait and self-rating assessments indicating impulsivity predicted proneness to sensitization. CONCLUSIONS: Sensitization to stimulants can be achieved in

healthy men in the laboratory. This phenomenon is associated with increased dopamine release and persists for at least 1 year.

American Journal of Psychiatry 2006 Dec; 163:2072-2079.

Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA.

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF METFORMIN TREATMENT OF WEIGHT GAIN ASSOCIATED WITH INITIATION OF ATYPICAL ANTIPSYCHOTIC THERAPY IN CHILDREN AND ADOLESCENTS

OBJECTIVE: Second-generation, or atypical, antipsychotics effectively treat psychiatric illness in children and adolescents. However, weight gain and abnormalities in insulin sensitivity, including diabetes, complicate this therapy. **METHOD:** A 16-week double-blind, placebo-controlled trial was conducted to evaluate the effectiveness of metformin in managing weight gain in 39 subjects, ages 10-17, whose weight had increased by more than 10% during less than 1 year of olanzapine, risperidone, or quetiapine therapy. Body weight, body mass index (kilograms per square meter of height), and waist circumference were measured regularly, as were fasting insulin and glucose levels. **RESULTS:** Weight was stabilized in subjects receiving metformin, while those receiving placebo continued to gain weight (0.31 kg/week). Because the study was conducted with growing children, metformin treatment resulted in reduction in z scores for both weight and body mass index.

The homeostasis model assessment, a surrogate indicator of insulin sensitivity, decreased in treated subjects. Overt diabetes was diagnosed in two subjects before treatment (elevated baseline fasting glucose and insulin values) and in two placebo-treated subjects (one at week 12 and the other after study completion). One subject taking placebo developed impaired fasting glucose. Placebo treatment was associated with the need to perform oral glucose tolerance testing upon study completion, by which three additional subjects were identified with impaired glucose tolerance. No serious adverse events resulted from metformin treatment. **CONCLUSIONS:** Metformin therapy is safe and effective in abrogating weight gain, decreased insulin sensitivity, and abnormal glucose metabolism resulting from treatment of children and adolescents with atypicals.

Acta Psychiatrica Scandinavica 2006 Nov; 114:346-351.

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MRI VOLUMETRIC AND 31P MRS METABOLIC CORRELATES OF CAUDATE NUCLEUS IN ANTIPSYCHOTIC-NAIVE SCHIZOPHRENIA

OBJECTIVE: To examine the volumetric and metabolic correlates of caudate nucleus in antipsychotic-naive schizophrenia patients in comparison with healthy controls. **METHOD:** Twelve antipsychotic-naive schizophrenia patients and 13 healthy controls underwent (31)P magnetic resonance spectroscopy of basal ganglia. Magnetic resonance imaging volume of caudate nuclei was measured using scion image software. **RESULTS:** Patients had significantly smaller caudate volume than healthy controls. Phosphocreatine (PCr)/total phosphorous and PCr/total adenosine tri-phosphate ratios of both caudate nuclei were significantly lower in patients than controls. Significant negative correlation was found between the left caudate volume and left PCr/total phosphorus ratio in the patients. Age at onset of psychosis had i) significant

negative correlation with right and left caudate volumes and ii) significant positive correlation with left PCr/total phosphorus ratio. **CONCLUSION:** The metabolic and volumetric abnormalities of caudate nucleus in antipsychotic-naive schizophrenia patients support neurodevelopmental etiopathogenesis.