METH- or MK-801-induced hyperactivity in rats and MK-801-induced PPI deficits in mice. TAK-063 at 0.1 mg/kg did not affect plasma prolactin levels and cataleptic response induced by HAL or OLA in rats.

Discussion: PDE10A inhibitors and HAL showed similar patterns of gene regulation in indirect pathway MSNs in mice. Combined treatment with TAK-063 and either HAL or OLA at subeffective doses produced significant antipsychotic-like effects but no augmentation of the plasma prolactin level and cataleptic response. Although further preclinical and clinical studies will be needed, TAK-063 may provide a novel mechanism as a PDE10A inhibitor for use as combination therapy in schizophrenia.

S224. DELTA-9-TETRAHYDROCANNABINOL CHALLENGE IN CANNABIS USERS AND NON-USERS DIFFERENTIALLY AFFECTS BRAIN FUNCTION AND BEHAVIOR: AN FMRI STUDY OF DEVELOPMENT OF TOLERANCE

Marco Colizzi^{*1}, Philip McGuire¹, Vincent Giampietro¹, Steve Williams¹, Mick Brammer¹, Sagnik Bhattacharyya¹

¹*Institute of Psychiatry, King's College*

Background: Cannabis use can induce acute and long-lasting psychosis and cognitive dysfunction. Some evidence suggests that the acute behavioral and neurocognitive effects of the main active ingredient in cannabis, (–)-trans-Δ⁹-tetrahydrocannabinol (Δ⁹-THC), might be modulated by previous cannabis exposure. However, this has not been investigated either using a control group of non-users, or following abstinence in modest cannabis users, who represent the majority of recreational users.

Methods: Twenty-four healthy men participated in a double-blind, randomized, placebo-controlled, repeated-measures, within-subject, Δ⁹-THC challenge study.

Results: Compared to non-users (N=12; <5 lifetime cannabis joints smoked), abstinent modest cannabis users (N=12; 24.5 ± 9 lifetime cannabis joints smoked) showed worse performance and stronger right hemispheric activation during cognitive processing, independent of the acute challenge (all $P \leq 0.047$). Acute Δ⁹-THC administration produced transient anxiety and psychotomimetic symptoms (all $P \leq 0.02$), the latter being greater in non-users compared to users ($P = 0.040$). Non-users under placebo (control group) activated specific brain areas to perform the tasks, while deactivating others. An opposite pattern was found under acute (Δ⁹-THC challenge in non-users) as well as residual (cannabis users under placebo) effect of Δ⁹-THC. Under Δ⁹-THC, cannabis users showed brain activity patterns intermediate between those in non-users under placebo (control group), and non-users under Δ⁹-THC (acute effect) and cannabis users under placebo (residual effect). In non-users, the more severe the Δ⁹-THC-induced psychotomimetic symptoms and cognitive impairments, the more pronounced was the neurophysiological alteration (all $P \leq 0.036$).

Discussion: Previous modest cannabis use blunts the acute behavioral and neurophysiological effects of Δ⁹-THC, which are more marked in people who have never used cannabis.

S225. A SYSTEMATIC REVIEW AND META-ANALYSIS OF PHARMACOLOGICAL INTERVENTIONS FOR REDUCTION OR PREVENTION OF WEIGHT GAIN IN SCHIZOPHRENIA

Sri Mahavir Agarwal^{*1}, Zohra Ahsan¹, Jonathan Lockwood¹, Marcus Duncan², Hiroyoshi Takeuchi¹, Tony Cohn¹, Valerie Taylor³, Gary Remington¹, Guy Faulkner², Margaret Hahn¹

¹*Centre for Addiction and Mental Health;* ²*University of British Columbia;* ³*Women's College Hospital*

Background: Weight gain is an extremely common problem in schizophrenia patients and is associated with morbidity and mortality. We conducted a Cochrane meta-analysis to determine the effects of pharmacological interventions aimed at reduction or prevention of weight gain in schizophrenia.

Methods: We searched the Cochrane Schizophrenia Group's Trials Register that is based on regular searches of CINAHL, BIOSIS, AMED, EMBASE, PubMed, MEDLINE, PsycINFO, and registries of clinical trials. There is no language, date, document type, or publication status limitations for inclusion of records in the register. We also searched reference sections within relevant papers, hand searched key journals, and contacted the first author of each relevant study and other experts to collect further information. We included all double blind randomized controlled trials examining any adjunctive pharmacological intervention for weight loss (treatment) or weight maintenance (prevention) in patients with schizophrenia or schizophrenia-like illnesses. We reliably selected, quality assessed and extracted data from studies. As endpoint and change data were combined in the analysis, mean differences (MD) of the change from baseline were calculated. The primary outcome measure was weight loss.

Results: Forty-four randomized controlled trials met the inclusion criteria for this review. Ten studies examined prevention of weight gain while on antipsychotics. Risperidone may be slightly effective in preventing weight gain (Weight: MD -2.09 kg, 95% CI -3.12 to -1.05; participants = 111; studies = 3; BMI: MD -0.70, 95% CI -1.03 to -0.36; participants = 111; studies = 3) and but the quality of evidence is low as the studies are small and have all been conducted by the same group. We are uncertain about the other agents used in a preventive role because the quality of evidence is very low.

Thirty-four studies examined reduction of weight gain with pharmacological interventions. Metformin is effective in bringing about modest weight loss (MD -3.45 kg, 95% CI -4.92 to -1.98 kg; participants = 569; studies = 8; BMI: MD -1.32 kg/m², 95% CI -1.84 to -0.81 kg/m²; participants = 606; studies = 9). This effect is probably stronger in first episode psychosis (FEP) patients (Weight: MD -5.18 kg, 95% CI -6.22 to -4.14 kg; participants = 214; studies = 3; BMI: MD -1.87 kg/m², 95% CI -2.19 to -1.56 kg/m²; participants = 214; studies = 3) compared to chronic patients (Weight: MD -2.0 kg, 95% CI -3.0 to -1.0 kg; participants = 355; studies = 5; BMI: MD -0.73 kg/m², 95% CI -1.04 to -0.42 kg/m²; participants = 392; studies = 6). Metformin probably decreases fasting insulin levels and insulin resistance as well. The frequency of adverse effects did not differ between metformin and placebo groups. Other agents that may reduce weight include aripiprazole, topiramate, H₂ antagonists such as nizatidine, and sibutramine but the quality of the evidence is low or very low making the effects uncertain. Importantly, none of the adjunctive treatment strategies result in higher dropout rates. Other than higher reports of anxiety with aripiprazole, none of the adjunctive treatment strategies appear to result in worsening of mental status.

Discussion: Accumulating evidence supports the safe use of pharmacological interventions to achieve modest weight loss. Risperidone may be slightly effective in preventing weight gain while metformin has the most evidence for use as treatment of weight gain in schizophrenia. The small number of studies, small sample size, and short study duration limits interpretation for other agents. Future studies that are adequately powered, with longer treatment duration, will be needed in evaluating the efficacy and safety of interventions for managing weight gain further.

S226. A STUDY COMPARING WEIGHT GAIN FROM ALKS 3831 TO OLANZAPINE IN EARLY-ILLNESS YOUNG ADULTS WITH SCHIZOPHRENIFORM, SCHIZOPHRENIA, OR BIPOLAR I DISORDER

Adam Simmons^{*1}, David McDonnell¹, Ying Jiang¹, Christine Graham¹, Bernard Silverman¹

¹*Alkermes, Inc.*