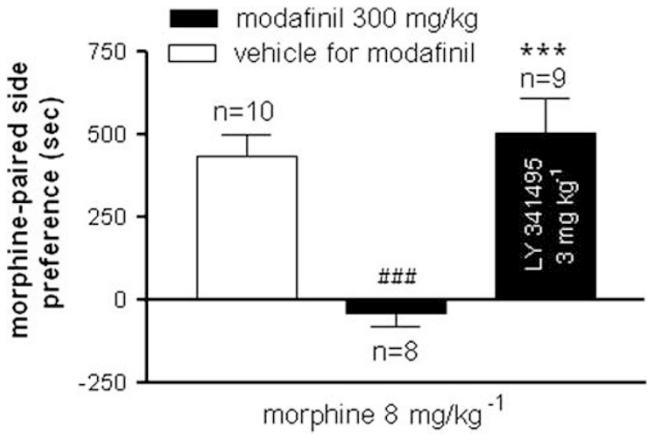

Figure 1. mGlu2/3 receptor blockade prevents the anti-relapse effects of modafinil. Rats were trained for conditoned place preference (CPP) with morphine (8 mg/kg) in a six-session conditioning protocol over 3 consecutive days. Animals were then exposed to extinction training, consisting of two daily 15-min preference tests without any treatment until the relative preference for the morphine-paired side decreased to $< +75$ s/15 min for four consecutive sessions. The reinstatement test (15 min) was conducted 24 h later. For the reinstatement test, animals received vehicle (left bar) or modafinil (300 mg/kg, i.p.; middle bar) 30 min before a priming injection of morphine (8 mg/kg) followed immediately by the preference test. Another group (right bar) was also pretreated with the mGlu2/3R antagonist LY341495 30 min before modafinil administration. Injection of LY341495 (3 mg/kg) completely reversed the anti-relapse effects of modafinil on morphine CPP. $^{###}p<0.001$ different from the control vehicle group (left bar) and $^{***}p<0.001$ different from the modafinil 300 mg/kg + morphine 8 mg/kg group (middle bar); there was no significant difference between the LY341495 + modafinil 300 mg/kg + morphine 8 mg/kg group and the morphine 8 mg/kg control group (left bar).

extinguished morphine conditioned place preference (CPP) in rats, extending the anti-relapse properties of modafinil to opiates (Tahsili-Fahadan *et al*, 2008). This anti-relapse effect of modafinil was blocked by administering an mGluR2/3 receptor antagonist, LY341495 (Figure 1), which is in line with previous findings, indicating the involvement of mGlu2/3 receptors in treatments for opiate and cocaine reinstatement in animal studies (Kalivas, 2009). This finding leads us to hypothesize that modafinil may block opiate relapse by stimulating mGlu2/3 receptors, effectively replacing the depleted tonic glutamate reservoir in the brain induced by chronic exposure to drugs of abuse, thereby preventing relapse to drug-seeking/taking (Kalivas, 2009).

In addition to this possible glutamate-mediated mechanism, modafinil is reported to affect other neurotransmitter systems such as catecholamines, serotonin, GABA, orexin, and histamine. The mild stimulant properties of modafinil may also be involved in its ability to reduce withdrawal symptoms of stimulant abuse. In a recent human PET study, modafinil was shown to block DA transporters and increase dopamine in the human brain including the nucleus accumbens (Volkow *et al*, 2009), in line with previous animal data. These and other findings highlight a potential for abuse of modafinil, although available data suggest a much lower potential for abuse and dependency than amphetamine-like stimulants (Myrick *et al*, 2004).

Altogether, modafinil shows promise as an anti-relapse medication. Nonetheless, its abuse potential and exact mechanism of action warrants further clinical and preclinical investigations.

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DISCLOSURE

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Trick or treat? neurodevelopmental consequences of pharmacotherapy for affective disorders

Drugs used to treat affective disorders exert their effects largely through their actions on various neurotransmitter systems. Neurotransmitters are important regulators of neural development. Thus, even limited periods of drug use/exposure during fetal- or postnatal brain ontogeny,

which continues to the end of the second decade, can, potentially, cause enduring, functionally significant changes in neuronal circuitry. The duration and timing of drug treatment are critical in determining long-term effects (Popa *et al*, 2008), owing to developmental changes in the neural substrates on which the drugs act.

Stress, which is associated with affective disorders, adversely impacts neural development during fetal life and postnatally, and is ameliorated by therapies that improve affect. Thus, potential, adverse, long-term effects of exposing the developing brain to medication must be weighed against the deleterious impact of stress elevation as a result of interrupted pharmacotherapy of pregnant women, or not treating children or adolescents.

Human studies have revealed few effects of fetal antidepressant drug (ADD) exposure that endure beyond infancy. By contrast, adult rodents exposed to ADDs only during stages corresponding to fetal life, childhood, or adolescence in humans exhibit a spectrum of abnormalities, many of which are, surprisingly, components of depression. Similar, long-term, 'mirror image' effects (that is, drug-induced increases in disease components that are reduced by pharmacological treatment of adults) occur after early-life anxiolytic treatment (Depino *et al*, 2008). Early exposure to atypical antipsychotic drugs, used to treat bipolar disorder in children and adolescents, induces significant, long-lasting cognitive deficits (Zuo *et al*, 2008) and morphological abnormalities (Frost *et al*, 2009).

Why do rodent and human data seem discrepant? In rodents, the behavioral syndromes induced by early ADD (Ansorge *et al*, 2008) or anxiolytic (Depino *et al*, 2008) treatment are progressive and emerge fully only in early adulthood. This is because early-life brain insults induce a cascade of effects over the course of development. Human studies of the effects on progeny of maternal ADD treatment during pregnancy so far reach only up to 7–10 years of age—too early to characterize long-term outcomes.

Early-life experience and environmental factors are emerging as additional, important modulators of the effects of psychotropic medications. We recently showed that, in rats, some of the enduring behavioral consequences of fetal exposure to fluoxetine do not occur if exposed infants are subjected to behavioral testing, which, by its nature, provides supplemental sensory stimulation and exercise (R Gibb, DO Frost and B Kolb, unpublished data). A provocative, parallel finding has recently been reported in humans: In infants who are not breast fed, maternal SSRI use during pregnancy is associated with altered hypothalamo–pituitary–adrenal (HPA) stress responses, whereas breast feeding abolishes this effect of fetal SSRI exposure by 3 months of age (Oberlander *et al*, 2008). The mode of feeding seems to act epigenetically: breast-fed infants have lower methylation (and probably higher expression) of the glucocorticoid receptor gene NR3C1 than nonbreast-fed infants (Oberlander *et al*, 2008).

Animal and human studies are consistent in demonstrating that environment and experience during fetal and postnatal brain maturation interact with early-life psychotropic drug exposure to shape the ontogeny of behavior and neural circuitry. Epigenetic modulation of gene expression appears to be one important mediator of these effects. These findings suggest possibilities for designing new therapeutic strategies that mitigate the effects of early-life ADD exposure.

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Ligand functional selectivity advances our understanding of drug mechanisms and drug discovery

'Intrinsic efficacy' (the concept that a drug acting at a single receptor is