Extended Abstract Journal of Clinical Medicine and Therapeutics 2020
Vol.5 No.3

Euro Neuropharmacology 2018 - Does Ritalin have the potential to become a drug of abuse? - Nachum Dafny - University of Texas

Nachum Dafny
The University of Texas Health Science Center at Houston, USA

The Methylphenidate (Ritalin), a stimulant medication treats attention deficit hyperactivity disorder (ADHD) and narcolepsy. Methylphenidate is a central nervous system (CNS) stimulant of the phenethylamine and piperidine classes. It was first discovered in 1944 and approved for medical use in United States in 1955. It may be taken by orally or applied to the skin. Psychostimulant Ritalin inhibits the reuptake of dopamine and norepinephrine, and increase dopaminergic and noradrenergic activity in the prefrontal cortex. Approximately 70% of people who use methylphenidate see improvements in ADHD symptoms. Children who use stimulant medications have longer attention spans. People with ADHD have an increased risk of substance use disorders without treatment, and stimulant medications reduce this risk. Some studies suggest that since ADHD diagnosis is increasing significantly around the world, using the drug may cause more harm than good in some populations using methylphenidate as a "study drug".This applies to people who potentially may be experiencing a different issue and are misdiagnosed with ADHD. People in this category can then experience negative side-effects of the drug which worsen their condition, and make it harder for them to receive adequate care as providers around them may believe the drugs are sufficient and the problem lies with the user. Methylphenidate is not approved for children under six years of age. Immediate release Ritalin is used daily along with the longer-acting form to achieve full-day control of symptoms. Ritalin is a stimulant with an addiction liability and dependence liability similar to amphetamine. It has moderate liability among addictive drugs; accordingly, addiction and psychological dependence are possible and likely when methylphenidate is used at high doses as a recreational drug. When used with the medical dose range, stimulants are associated with the development of stimulant psychosis. Methylphenidate can also be used for off-label use in treatment-resistant cases of bipolar disorder and major depressive disorder. Therapeutic doses of amphetamine and methylphenidate result in modest improvements in cognition, including working memory, episodic memory, and inhibitory control, in normal healthy adults; the cognition-enhancing effects of these drugs are known to occur through the indirect activation of both dopamine receptor D1 and adrenoceptor α2 in the prefrontal cortex. Inattention and impulsivity are the key behaviors of ADHD. Some people with ADHD have problems with the behavior, while others have both inattention and hyperactivity-impulsivity. Excessive doses of methylphenidate, above the therapeutic range, can interfere with working memory and cognitive control. Methylphenidate increases stamina in humans primarily through reuptake inhibition of dopamine in the central nervous system. Methylphenidate can worsen psychosis in people who are psychotic, and in very rare cases it has been associated with the emergence of new psychotic symptoms. It should be used with extreme caution in people with bipolar disorder due to the potential induction of mania or hypomania. There have been very rare reports of suicidal ideation, but some authors claim that evidence does not support a link. Logorrhea is occasionally reported. Libido disorders, disorientation, and hallucinations are very rarely reported. Priapism is a very rare adverse event that can be potentially serious. Methylphenidate has the potential to induce euphoria. At therapeutic doses, the reward pathway in particular, to the extent necessary to cause persistent increases in ΔFosB gene expression in the D1-type medium spiny neurons of the nucleus accumbens; consequently, when taken as directed in doses that are commonly prescribed for the treatment of ADHD, methylphenidate use lacks the capacity to cause an addiction. However, when methylphenidate is used at sufficiently high recreational doses through a bioavailable route of administration (e.g., insufflation or intravenous administration), particularly for use of the drug as a euphoriant, ΔFosB accumulates in the nucleus accumbens. Methylphenidate is most active at modulating levels of dopamine (DA) and to a lesser extent norepinephrine. Methylphenidate binds and blocks dopamine transporters (DAT) and norepinephrine transporters. Variability exists between DAT blockade, and extracellular dopamine, leading to nonresponse in those with low basal DA activity. On average, methylphenidate elicits a 3–4 times increase in dopamine and norepinephrine in the striatum and prefrontal cortex. MRI studies suggest that long-term treatment with ADHD stimulants decreases abnormalities in brain structure and function found in subjects with ADHD. Both amphetamine and methylphenidate are predominantly dopaminergic drugs, yet their mechanisms of action are distinct. Methylphenidate acts as a norepinephrine–dopamine reuptake inhibitor, while amphetamine is both a releasing agent and reuptake inhibitor of dopamine and norepinephrine. Methylphenidate's mechanism of action in the release of dopamine and norepinephrine is fundamentally different from most other phenethylamine derivatives, as methylphenidate is thought to increase neuronal firing rate, whereas amphetamine reduces firing rate, but causes monoamine release by reversing the flow of the monoamines through monoamine transporters via a diverse set of mechanisms, including TAAR1 activation and modulation of VMAT2 function, among other mechanisms. The difference in mechanism of action between methylphenidate and amphetamine results in methylphenidate inhibiting amphetamine's effects on monoamine transporters when they are co-administered. Methylphenidate has both dopamine transporter and norepinephrine transporter binding affinity, with the dextromethylphenidate enantiomers displaying a prominent affinity for the norepinephrine transporter. Treatment of children with MPD for extended periods of time when they are going through neurodevelopmental processes modulates these critical neurodevelopmental processes that may alter the body's homeostasis. Moreover, since

This work is partly presented at 10th World Congress on Neuropharmacology August 28-29, 2018 Paris, France

chronic MPD use can elicit behavioral withdrawal, sensitization, or tolerance, psychostimulant therapy given to adolescents and young adults may increase the risk for Substance Use Disorder. While, other reports suggest that psychostimulant treatment in adolescence for ADHD protects them from developing a future Substance Use Disorder. These contradictory reports call for basic in-depth studies to resolve this critical issue. Both the dextrorotary and levorotary enantiomers displayed receptor affinity for the serotonergic 5HT1A and 5HT2B subtypes, though direct binding to the serotonin transporter was not observed. Behavioral sensitization and behavioral tolerance following the same chronic MPD dose of 0.6, 2.5, or 10.0 mg/kg exposure were observed. Expression of behavioral sensitization or tolerance following chronic psychostimulant exposure suggests that the drug has the potential to elicit dependence (addiction).

This work is partly presented at 10th World Congress on Neuropharmacology August 28-29, 2018 Paris, France