# Adderall XR® and Vyvanse™

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## ABSTRACT

Adderall XR® (MAS XR) and Vyvanse™ (LDX) are both schedule II amphetamine-based central nervous system stimulants indicated for the treatment of attention-deficit/hyperactivity disorder. Differences among the two primarily involve dosage form, pharmacokinetic profiles, and abuse potential. MAS XR and LDX are both long-acting stimulants with an approximate duration of action of 10 hours. The long-acting property of LDX is secondary to its prodrug formulation, whereas MAS XR utilizes bead filled capsules that mimic twice daily dosing upon administration. MAS XR is a substrate of CYP 2D6 while LDX does not utilize the cytochrome P450 enzymes for metabolism. There are few efficacy studies that directly compare LDX and MAS XR. There are no head to head abuse liability studies for MAS XR and LDX; however, the prodrug formulation of LDX is proposed to have lower abuse potential.

## KEYWORDS

Attention-deficit/hyperactivity disorder, stimulant, amphetamine

## INTRODUCTION

Adderall XR® (dextroamphetamine/amphetamine) (MAS XR) and Vyvanse™ (lisdexamfetamine) (LDX) are both categorized as central nervous system (CNS) stimulants indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients 6 years of age and older. MAS XR is the older of the two products, which was initially approved in 2001 while LDX was initially approved in 2007.[1,2] Each of these CNS stimulants is further classified as an amphetamine product. Variability between the two medications may exist with regards to their pharmacokinetics and abuse potential. There are limited data directly comparing the efficacy of these two medications. This review will compare MAS XR and LDX with regards to their pharmacokinetics, efficacy, and abuse potential.

## PHARMACOKINETICS

Both MAS XR and LDX are long-acting, once daily stimulants with a duration of action of approximately 10 hours. Long-acting stimulants are considered to be equally efficacious to the short acting stimulants (i.e., immediate release MAS).[3] MAS XR is a bead filled (mixed amphetamine combination) capsule that upon administration mimics twice daily dosing. Half of the beads in the MAS XR capsule are immediate release while the other half are extended release.[3] MAS XR reaches its peak plasma concentration in approximately 7 hours, which is consistent with its extended release properties.[2] The long acting property of LDX is secondary to it being a prodrug of dextroamphetamine making it the only prodrug stimulant. A prodrug is a product that when initially administered is inactive but then undergoes biotransformation in the body to have a therapeutic effect. After oral administration, LDX is cleaved into L-lysine, an essential amino acid, and dextroamphetamine.[4] This conversion is proposed to occur primarily (90%) in systemic circulation.[5] LDX reaches its peak plasma concentration in approximately 1 hour while the active medication, dextroamphetamine, reaches a peak plasma concentration in approximately 3.5 hours.[1] Both MAS XR and LDX display linear pharmacokinetics in a dosage range of 5-30 mg and 30-70 mg in children 6-12 years of age. While food does not affect the extent of absorption for either medication, it has been shown to prolong the time to maximum concentration by 2.5 hours for MAS XR and 1 hour for LDX.[1,2] The enzymes involved in MAS XR metabolism have not been clearly defined; however, CYP2D6 is known to be responsible for the formation of one of the MAS XR active metabolites, 4-hydroxy-amphetamine. The other active metabolite of MAS XR is norephedrine.[2] Intact LDX does not utilize the cytochrome P450 enzymes for metabolism.[1] Any drug interactions associated with LDX are thought to be secondary to amphetamine and its metabolites and not to intact LDX. In vitro studies of amphetamine and its metabolites indicate minor inhibition of CYP2D6, 1A2, and 3A4.[1,5]

## EFFICACY

There are many clinical trials establishing the efficacy of individual long-acting stimulants in both pediatric and

adult patients.[6] In the literature, there are also comparison studies of various amphetamine and methylphenidate products; however, direct efficacy comparison studies of LDX and MAS XR are limited.[7] Biederman et al. conducted a randomized, multicenter, double-blind, placebo- and active-controlled, cross-over study with MAS XR included as a reference arm. This study was not designed to directly compare the efficacy of MAS XR and LDX but to evaluate the efficacy and safety of LDX in children 6-12 years of age with a diagnosis of ADHD. Subjects in this study were initiated on MAS XR 10 mg/day and titrated to an individualized optimal daily dose over a period of 3 weeks. After the initial 3 week period, subjects then entered the double-blind crossover part of the study. The subjects each received 1 week of placebo, 1 week of the optimized MAS XR daily dose (10, 20, or 30 mg/day), and 1 week of the equivalent LDX daily dose (30, 50, 70 mg/day). The order in which they received these treatments was randomized. The primary efficacy measure was the Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment Rating Scale (SKAMP-DS). Secondary efficacy measures included SKAMP-AS (attention), Permanent Product Measure of Performance—Attempted (PERMP-A) and Correct (PERMP-C) scores, and Clinical Global Impression (CGI) scales. With regards to the primary efficacy measure, MAS XR and LDX significantly improved the SKAMP-DS score when compared to placebo. Mean SKAMP-DS scores were 0.8 ± 0.1 for both MAS XR and LDX and placebo-treated subjects had a mean SKAMP-DS score of 1.7 ± 0.1 ($p < .0001$).[8]

## ABUSE POTENTIAL

Among the college population, nonmedical use of prescription medications represents the second most common form of illicit drug use. The University of Michigan's Monitoring the Future study reports a 5.7% rate of nonprescription methylphenidate use among college students.[9] Both MAS XR and LDX are classified as schedule II controlled substances by the United States Drug Enforcement Agency (DEA).[5] Drug "liking" and euphoria may be associated with a faster rate of absorption and delivery to the brain. By controlling the rate of absorption (i.e., extended release capsule, prodrug formulation), the potential for stimulant abuse may also be decreased. However, long acting stimulants are not free of abuse potential. Formulations such as MAS XR may be manipulated (i.e., crushed, melted, dissolved) in order to increase the absorption via intranasal or intravenous routes.[6] Head-to-head abuse liability studies of MAS XR and LDX have not been done.[7] Although, still classified as a schedule II controlled substance, LDX is proposed to have a lower abuse potential secondary to its prodrug formulation. Unlike MAS XR, LDX capsules do not contain free or active dextroamphetamine. In order to be converted to its active component, dextroamphetamine, LDX requires enzymatic hydrolysis at which point a slow rise in dextroamphetamine occurs. There are various discussion forums and other Internet resources which describe how to chemically extract dextroamphetamine from LDX.[10] These discussion forums are not considered a professional resource and the methods described as well as the information given cannot be verified. These methods are more labor intensive than what is seen with stimulants such as MAS XR that contain free or active dextroamphetamine. If LDX capsules are physically manipulated, the prodrug remains chemically intact. Intranasal or intravenous administration would still result in a delayed peak unless the user was able to extract dextroamphetamine by enzymatic hydrolysis. This property of LDX is thought to decrease the abuse potential; however, it is still classified as a schedule II controlled substance with high abuse potential and should be monitored as such. The abuse potential for LDX has been evaluated in two human studies. In a double blind, placebo controlled, crossover study, 38 non-ADHD subjects with a history of stimulant abuse received single oral doses of 50, 100, or 150 mg of LDX, 40 mg of immediate release dextroamphetamine, and 200 mg of diethylpropion hydrochloride. Using the Drug Rating Questionnaire-Subject Liking Scale as a primary measure, LDX 100 mg produced significantly less drug liking effects when compared to dextroamphetamine 40 mg. The higher dose of LDX, 150 mg, had a similar drug liking score as the 40 mg dextroamphetamine dose; however, the peak effect was 2 hours later than the immediate release dextroamphetamine. This may be reflective of the formulation of LDX.[1,4] When comparing 50 mg of IV LDX to an equivalent dose (20 mg) of IV dextroamphetamine, the liking effect of LDX was more than placebo but less than what was produced by the 20 mg IV dextroamphetamine dose.[1,4]

## COST

Other differences in MAS XR and LDX are generic availability and cost. MAS XR is available in brand and generic 5, 10, 15, 20, 25, and 30 mg capsules. Brand MAS XR is approximately $854.75 and generic is approximately $613.15, each in bottles of 100. There is no generic available for LDX. LDX is available as 20, 30, 40, 50, 60,

and 70 mg capsules. Each bottle of 100 capsules is approximately $730.36.[11,12]

## CONCLUSION

LDX and MAS XR are both schedule II controlled substances, utilized as first line agents for the treatment of ADHD in patients 6 years of age and older. While each of these medications has been shown to be effective for ADHD, the primary difference between the two is their formulation. Both MAS XR and LDX are considered long acting stimulants. However, their mechanism of long acting activity is different. MAS XR is an extended release capsule that when given once daily, mimics twice daily dosing. LDX is a prodrug that requires enzyme hydrolysis to convert to its active form. The prodrug formulation of LDX aids in less pharmacokinetic variability and potentially less abuse potential.[4]

When considering the choice of MAS XR and/or LDX one must consider the patient population being treated. The key difference between MAS XR and LDX is their potential for abuse. In an inpatient facility it may not be cost effective to have LDX on formulary, particularly when the medications are administered and monitored by inpatient staff. Another factor to consider when treating inpatients is whether or not the patient has been stabilized on MAS XR or LDX as an outpatient. If a patient is stable on their current regimen for ADHD it is wise to consider keeping the regimen the same, especially if admitted for non-psychiatric reasons. In cases where patients are being treated as outpatients, the use of LDX may be advantageous in order to decrease the risk for potential drug abuse particularly when the patient being treated has a history of intranasal or intravenous substance abuse.

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