Project on Drug Development
Drug chosen: Amphetamine
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(A) Lead Compound Discovery

Although amphetamine was first synthesized in 1887 by the Romanian Lazar Edelearnu in Berlin, no pharmacological use was found for the drug until 1927. In 1927, Gordon Alles resynthesized it and it was used as a decongestant, replacing ephedrine. However, it was just for non-medical purpose at that time.

(B) Formulation Development

Amphetamine has long been used as a psychostimulant which can increase wakefulness and combat fatigue. So far, there are three popular brands of drugs containing amphetamine as active ingredient. They are *Adderall, Vyvanse and Dexedrine*.

Adderall was originally developed by Shire Pharmaceuticals in 1996. In 2006, it was sold to another manufacturer Teva Pharmaceuticals. Dextroamphetamine and racemic DL-amphetamine salts were included in *Adderall* as the active ingredients. *Adderall* is now available in 2 formulations: immediate release and extended release. These 2 formulations exhibit a strong effect on DL-amphetamine absorption and excretion.

Lisdexamfetamine is sold as *Vyvanse*, which was developed by New River Pharmaceuticals in 2005. Dextroamphetamine and levoamphetamine were included in *Lisdexamfetamine* as the active ingredients. The available formulation includes pill formulation of various dosages. This is a single-enantiomer amphetamine formula which can reduce side effects.

Dexedrine contains dextroamphetamine sulfate salt was used as the active ingredient. The available formulations include tablet and sustained-release capsule. The formulations are able to exhibit preventive effect on the neurotransmitters, leading to a prominent reduction of fatigue.

(C) Molecular Modification

Amphetamine, 1-phenylpropan-2-amine, was first synthesized from ephedrine, 2-methylamino-1-phenylpropan-1-ol.

Adderall is actually prepared by a group of mixed amphetamine salts. Amphetamine is modified to racemic amphetamine aspartate monohydrate, dextroamphetamine saccharide, detroamphetamine sulfate as well as racemic amphetamine sulfate.

For the preparation of *Lisdexamfetamine*, amphetamine is first modified to dextroamphetamine, and then converted to lisdexamfetamine. Dextroamphetamine salt is dissolved to dissociate ions and the covalent amide bonds of dextroamphetamine ions undergo hydrolysis. Hence, lisdexamfetamine, (1S)-1-methyl-2-phenylethyl-L-lysinamide, is formed as the final product.

Since active ingredient of Dexedrine is dextroamphetamine, amphetamine is converted to dextroamphetamine, (S)-1-phenylpropan-2-amine, for the preparation of Dexedrine. In fact, dextroamphetamine is an enantiomer of amphetamine.

(D) Safety Tests and Human Trials

Adderall

Compared with *Adderall* immediate release, more trial tests have been performed on *Adderall* extended release. *Adderall XR* exhibited a better tolerability during the human trial at all dosages. A two-year trial test has been carried out by Harvard Medical School investigators at Massachusetts General Hospital. This trial shows that adults with Attention Deficit Hyperactivity Disorder (ADHD) experienced significant long-term ADHD symptom control when treated with once-daily *Adderall XR*.

The average age of participants was 40 and all had a history of ADHD before age 7. Of the participants, about 60 percent were men and 90 percent were Caucasian. Many of the participants were not diagnosed until they were adults and reported that their symptoms had negatively impacted their lives prior to treatment. At the end of the trial, an evaluation of the validated Quality of Life Enjoyment and Satisfaction Questionnaire Medication Satisfaction test revealed that patients were significantly satisfied with their treatment.

Vyvanse

A long-term open-label extension trial has been carried out by American Psychiatric Association. The results show that patients taking *Vyvanse* experienced an improvement in the symptoms of ADHD after one year of treatment. Based on the participants' average change in ADHD Rating Scale scores, the mean scores decreased from baseline by 63%. Additionally, 95% of patients who received 12 months of daily treatment were rated as "very much improved" or "much improved" by physicians.

All 272 patients in the long-term trial have previously participated in either of two double-blind clinical trials of *Vyvanse*. In the long-term trial, investigators provided participants with 30 mg once-daily doses of *Vyvanse* for one week, and then adjusted the dosage by 20 mg at weekly intervals during three subsequent visits to achieve optimal efficacy and tolerability. Participants continued treatment for the remaining 11 months.

Safety was also evaluated during the study and *Vyvanse* was generally well tolerated. Most treatment-associated side effect were mild to moderate in severity, occurred during the first eight weeks of treatment and incidence decreased over time. The most frequently reported side effects in this trial were decreased appetite, headache, decreased weight and insomnia.

Dexedrine

Prescribed in the treatment of ADHD or narcolepsy, the human trial shows that dextroamphetamine can help improve attention span and behaviour by influencing the central nervous system. However, there is no test that can show how it works exactly until now. Besides, safety tests of dextroamphetamine on treating other mental illness show that it can be successfully applied in the treatment of certain kind of depression and psychiatric syndrome. Tests also show successful prescription for reducing fatigue in cancer patients and depression in HIV patient. Yet, these types of prescription are still at the experimental stage.

(E) Approval for Marketing

Adderall

In 2001, Shire Pharmaceuticals has been granted the US patent for *Adderall* XR. So far, the immediate formulation of *Adderall* has been approved for the treatment of ADHD as well as narcolepsy. However, since the XR formulation consists of potential addictive property and powerful ability to raise blood pressure, it is a Schedule II drug under the Controled Substance Act. Therefore, this formulation has only been approved for the treatment of ADHD. In comparison, *Vyvanse* is preferred more than *Adderall* for the prescription owing to the lower misuse potential.

Vyvanse

On 23th February 2007, *Vyvanse* has received the approval from the U.S. Food and Drug Administration (FDA) for the treatment of ADHD. The available dosage strengths include 30mg, 50mg and 70mg at that time.

On 3rd January 2008, 20mg, 40mg and 60mg strength pills has also received the approval from the FDA. These 3 dosages have supplement the previous 3 dosage strength.

On 19th February 2009, 30mg and 5mg strength capsule formulations have received approval from Health Canada as well. However, it still has not been on sale yet.

Dexedrine

The control-release formulation has been approved by the FDA for the treatment of ADHD as well as narcolepsy. However, prescription for the treatment of depression and weight loss has been rarely recommended.