Preface

Depression is a state of mind or, more specifically a mental disorder characterized by a lowering of the individual's vitality, mood, desires, hopes, aspirations and self esteem. It may range from no more than a mild feeling of tiredness and sadness to the most profound state of apathy with complete, psychotic disregard for reality. With its various manifestations depression can be the only symptom complex an individual may show and thus constitute a mental disorder in itself. Depression can also precede or be a part of other illnesses, such as schizophrenia, senile or arteriosclerotic brain disorder and of serious metabolic diseases (Mendelssohn 1964).

Oral administration of antidepressants is the most commonly available therapy at present to get rid off from depression. Antidepressants work by controlling the balance of the neurochemistry in the brain. They work by excitatory mechanism of brain chemicals and when once treatment is discontinued, the patients may attain normal situation but still side effects are carried further. Depression and heart diseases often travel together, which is why study of depression and antidepressants are gaining importance. Antidepressants may raise a heart patient's risk of dying in 3 years (Altar 1999; Harrar and Gould 2006) because depression itself lowers survival rates (Watkins 2007). According to Smith (2007) antidepressants are not happy pills and they are not a panacea. They are prescription only, drugs that come with risks as well as benefit.

Antidepressants prescribed for depression fall in to following four different classes of drugs.

a. Selective Serotonin Reuptake Inhibitors (SSRIs)
b. Tricyclic Antidepressants (TCAs)
c. Monoamine Oxidase Inhibitors (MAOIs)

d. Selective Norepinephrine Reuptake Inhibitors (SNRIs).

Each class of antidepressants has various side effects associated with them. For example, SSRIs can cause an increase in suicidal thoughts and behavior. They also carry a risk for increased hostility, agitation and anxiety. In adults who are 65 and older, SSRIs increase the risk for falls, fracture and bone loss. The SSRIs can also cause serious withdrawal symptoms if the intake of drug is stopped. Similarly TCAs although reduce depression also partially inhibit the re absorption of dopamine. Because the TCAs have such a broad mechanism of action, they tend to cause more side effects. MAOIs have severe interactions with certain foods, drinks and medications. Combining MAOIs with foods or drinks containing tyramine can result in dangerously high blood pressure, which can lead to a stroke or heart attack. Because of this danger, MAOIs are not typically chosen as a first line depression treatment. SNRIs, which target other neurotransmitters either alone or in addition to serotonin affect some of brain chemicals affect including norepinephrine and dopamine.

Antidepressants though target neurotransmitters and mainly their action is on 5HT receptors which results in various side effects and the most common and severe side effect is on sexual function. This may cause impotence and or delayed ejaculation in males and the inability to reach orgasm in women (Anonymous 2006). Long term use of the SSRIs may lead to increased risk for breast cancer (Morgan 2005). Antidepressants are responsible for other physiological changes in the body, specifically in the extrapyramidal system. Some physiological changes that may occur in this system as a result of antidepressant medication are akathisia (a compulsive restlessness), dystonias (sudden, jerky movements) and akinesia (reduced
movement). These extra pyramidal effects are somewhat rare and may cause long-term problems in the individuals (Palfai and Jankiewicz 2001). Antidepressant also involves physiological effects when a pregnant mother uses during last trimester. Physiological reactions in the newborn include, but are not limited to, premature delivery, low birth weight, respiratory distress, cyanosis, apnea, seizures, instable temperature, feeding difficulty, vomiting, hypoglycemia, hypotonia, jitteriness, diminished pain reactivity, irritability, and constant crying (Palfai and Jankiewicz 2001; Tamam and Ozpoyraz 2002).

Many studies indicate that chronic administration of antidepressants downregulate or reduce the density of (5HT\textsubscript{2} binding sites in rat frontal cortex. These adapting sites are sited as necessary for antidepressant response (Cowen \textit{et al} 1994). The (5HT\textsubscript{2}) agonists (including SSRI receptors) contribute to sexual dysfunction, anxiety, and insomnia. To date, findings remain somewhat inconclusive as to the exact nature.

Another possible mechanism whereby antidepressants may change the physical relationship between neurons in the brain is by inhibiting neurite outgrowth from nerve cells. Amitriptyline inhibits neurite outgrowth from chick embryonic cerebral explants in vitro (Wong \textit{et al} 1991). A common mode of action of all antidepressants could be to modify the actual structure of nerve cells and possibly eliminate inappropriate synaptic contacts that are responsible for behavioral and psychological changes associated with depression.

Adverse effects of SSRIs include ejaculation failure, drymouth, sweating, somnolence, tremor, dizziness, fatigue, dyspersia, insomnia, paresthesia, anxiety, nervousness and abnormal vision. Other events observed during the premarketing
evaluation of sertraline are impotence, flushing, increased saliva, mydriasis, vasodilation and other male sexual dysfunction. Other events observed during post marketing evaluation are acute renal failure, anaphylactoid reaction, bradycardia, serotonin syndrome, in some patients elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

Long-term administration of a variety of antidepressant treatments, including TCAs, MOAIs and electroconvulsive shock, seem to downregulate or desensitize the BARs in rat forebrain (Sulser 1984) and enhance the synaptic efficacy of serotonergic neurotransmission via the 5HT1A receptor in rat hippocampus (Chaput et al 1991). Recent studies have investigated the effects of long term administration of antidepressants on the levels of G protein subunits. Overall, the results are far from conclusive and have tended to reveal a complex, regional- and tissue-specific pattern of effects on various G proteins a subunit and their mRNA levels after long term treatment with various antidepressants (Lesch and Manji 1992). In recent years, it has become increasingly appreciated that any relevant biochemical models proposed for the effects of many psychotropic drugs (including mood stabilizers, antidepressants, and antipsychotics) must account for their special temporal clinical profile, in particular that the therapeutic effects require a lag period for onset of action and are generally not immediately reversed on drug discontinuation. Patterns of effects requiring such prolonged administration of the drug suggest alterations at the genomic level (Jope 1999).

Thus the above review of literature shows that although the antidepressants are routinely prescribed they have variety of effects involving both nervous and other systems. Although some routine preliminary tests are conducted before the release of these drugs for commercial use, their effect on the behavior will not be included in
such preclinical tests. As their action is on the nervous system, their effect on behavior cannot be ignored. The only study that has been carried out so far is by Nazari (2004) where he has studied the effects of two antidepressant drugs, fluoxetine and amitriptyline on the sexual behavior of Drosophila where he has reported that the drugs when administered affect the male sexual behavior. The observation of Nazari (2004) has led the author to propose the hypothesis that the antidepressants have sex specific action. The present study is proposed by the author to test this hypothesis.

Drosophila is a remarkable insect; in addition to serving as an important laboratory tool for genetic studies, responds to psychoactive drugs, demonstrating molecular and behavioral patterns that are essentially indistinguishable from those in mammals (Chin and Svetlana, 2002). The fly is currently the model organism that allows the most sophisticated genetic manipulations of all higher eukaryotes. An arsenal of genetic tools permits the investigation of the complexity of the nervous system in unprecedented detail. Drosophila research has contributed to our understanding of nervous system development (Doe 2008; Hartenstein et al 2008) growth cone guidance and target recognition (Dickson 2002) synapse remodeling (Collins and Diantonio 2007) and the neural circuitry underlying behaviors such as courtship (Villella and Hall 2008). Equally important is characterization of genes, and their products, that act in defense toward individual or classes of toxic compounds. The sum of these well-documented developmental and behavioral aspects of Drosophila makes it an especially informative and adaptable model to investigate a wide variety of toxicological endpoints relevant to human biology and behavior.

The review of literature thus shows that the knowledge on the effects of antidepressants is incomplete and thus raises certain questions they are, whether the effects of antidepressant drugs are short term or long term? Preliminary reports are
already available showing that the antidepressant drugs lead to over expression of certain proteins. Because the antidepressants have excitatory function on brain chemicals, the most obvious question is whether they have any effect on an individual’s behavior. To address these questions, the present investigations have been planned using *Drosophila melanogaster* as the test system. The objectives of the present study were to analyze,

1. The toxic effects of one antidepressant drug from each class of antidepressants and to study the effect of these antidepressants on the sexual behavior of *D.melanogaster*.
2. The effect of these antidepressants on the fitness and viability of *D.melanogaster*.
3. The effect on the transcription through analysis of puffing pattern in the polytene chromosomes of *D.melanogaster* and
4. The effect of the drugs on the expression of esterase enzymes.

The results obtained by the author on the above objectives have been presented in the four chapters of this thesis.