IJPSR (2013), Vol. 4, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 October, 2012; received in revised form, 05 December, 2012; accepted, 26 January, 2013

ANXIETY AND DEPRESSION: ADVANCES IN MANAGEMENT OF DISORDER

Aakruti Kaikini*, Swati Dhande, Kalpana Patil and Vilasrao Kadam

Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D. Belapur, Navi Mumbai-400614, Maharashtra, India

Keywords:

Anxiety, Depression, Neurobiology, HPA Axis, current advances

Correspondence to Author:

Aakruti Kaikini

Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D. Belapur, Navi Mumbai-400614, Maharashtra, India

E mail: aakruti.kaikini@gmail.com

ABSTRACT

Anxiety and depression is basically a disorder of the present modern world and its prevalence is seen increasing day by day. According to WHO, anxiety and depression will be the second largest cause of disability worldwide by year 2020. The major problem associated with this disorder is that common masses are unaware about this disorder and hence less than 25% of those affected have access to appropriate treatments. The medications currently used for treatment of this disorder are based on the earlier theories of anxiety and depression. These medications have many side effects as well as are associated with tolerance and dependence on prolonged usage. This article mainly focuses on the new theory involved in neurobiology of this disorder and drugs which can be developed on basis of the same.

INTRODUCTION: Anxiety and depression is basically a disorder of the present modern world and its prevalence is seen increasing day by day. This is more so in today's fast paced and competitive world

The root meaning of the word anxiety is 'to vex or trouble. Anxiety is a psychological and physiological state characterized by somatic, emotional, cognitive, and behavioural components [1]. It is the displeasing feeling of fear and concern [2]. Anxiety is basically a normal reaction to a stressor and helps us to deal with a difficult situation by prompting us to cope with it. However when anxiety becomes excessive, it may fall under the classification of an anxiety disorder [3].

Depression can be defined as a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being [4]. According to WHO, anxiety and depression will be the second largest cause of disability worldwide by year 2020. It is also associated with loss of approx. 8, 50,000 lives every year and affects about 121 million people worldwide.

The major problem associated with this disorder is that less than 25% of those affected have access to appropriate treatments.

A cross-cultural study conducted by WHO at 14 sites to study prevalence of mental disorders in primary care settings across the sites showed the prevalence of depression in Bangalore was 9.1% [5].

With a population of approx. 103 crores per the 2001 census, projecting the Bangalore figures to the total Indian population, the number of depressed patients in India can be computed to be approximately 9 crores [6].

Sex, age and race are the factors which govern the onset of this disorder. Women are more likely than men to experience this disorder during their lifetime.

Compared to adults above the age of 60 years, younger population is more likely to suffer from this disorder. Non- Hispanic blacks are less likely than Non-Hispanic whites to experience this disorder during their lifetime [7].

Neurobiology of Anxiety and Depression: The early theories for anxiety and depression focussed on the levels of neurotransmitters in certain regions on brain.

The "monoamine hypothesis" proposed by Schildkraut in 1965 states that depression is caused by functional deficit of monoamine neurotransmitters at certain sites in brain while anxiety is caused to due disturbance in levels of certain neurotransmitters in brain. The main neurotransmitters involved are serotonin, noradrenaline, GABA.

Serotonin originates in the raphae nucleus of brain stem and projects throughout forebrain prefrontal cortex and limbic system. Its release is responsible for producing anxiolytic effect.

Noradrenaline originates in locus ceruleus and projects throughout forebrain prefrontal cortex and limbic system. Its release is responsible for producing anxiogenic effect. GABA is the major inhibitory neurotransmitter in brain found virtually in all areas of brain. Its release is responsible for anxiolytic effect [8, 9].

The above mentioned theories for anxiety and depression have several limitations. It fails to explain the complex aetiology of disease as well as co-existence of anxiety and depression. It is also evident that neurotransmitter precursors do not have antidepressant or anxiolytic effect. There is no impairment in synthesis of these neurotransmitters nor is there any excessive degradation of these neurotransmitters. A lag time of few weeks is required for the drugs to exert their clinical effects. This suggest that changes in levels of neurotransmitters occurs secondary in anxiety and depression.

Current research has led to the suggestion that primary mechanism involved in anxiety and depression is "Dysregulation of Hippocampus-Hypothalamic-Pituitary Adrenal axis (HPA Axis)". The main anatomical regions involved in anxiety and depression are hippocampus and amygdala. The hippocampus and amygdala govern emotions and memory. There are anatomical projections between hippocampus, amygdale and hypothalamus. Sensory information enters lateral amygdala where it is processed and passed to the central nucleus, the major output nucleus of amygdala.

The central nucleus projects to multiple brain systems responsible for producing physiologic and behavioural responses to fear. Projections to hypothalamus activate the sympathetic nervous system. Neurons in the paraventricular nucleus (PVN) of hypothalamus secrete corticotrophin releasing factor (CRF). CRF acts on postsynaptic CRF1 receptors.

Activation of CRF1 receptors is associated with anxiety and depressive symptoms. CRF also stimulates the synthesis and release of adrenocorticotrophin (ACTH) from anterior pituitary by activation of CRF receptors. ACTH stimulates the synthesis and release of glucocorticoids from adrenal cortex (cortisol in humans and corticosterone in rodents) [10 11]. These affect metabolism and behaviour via direct actions on numerous areas of brain.

Cortisol induced effects	CRF induced effects
Cognitive disturbance	Anxiety
Affective syndromes	Psychomotor activity
Psychotic symptoms	Anorexia
Supressed neurogenesis	Loss of libido
Metabolic syndrome	Sleep disturbance

HPA axis is controlled by [9]:

1) Hippocampus : it exerts an inhibitory influence on hypothalamic CRF containing neurons via polysynaptic circuit by release of inhibitory neurotransmitters such as GABA

2) Amygdala :exerts a direct excitatory influence on hypothalamic CRF containing neurons

3) Monoanimenergic transmission exerts inhibitory influence on hypothalamic CRF containing neurons [12].

Glucocorticoids including synthetic forms like dexamethasone repress CRF and ACTH synthesis and therefore inhibit their own synthesis by action on hippocampal neurons, particularly cA3 pyramidal neurons (feedback inhibition). However sustained elevation of glucocorticoids under prolonged and severe fear damages this feedback inhibition and causes destruction of hippocampal neurons. The resulting hypercortisolimaea causes decrease in dendritic branching to glutaminergic synaptic inputs increasing glutaminergic activity.

CRF also directly acts on NMDA type of glutamate receptors and increases excitability of basolateral nucleus neurons responsible for symptoms of anxiety [13, 14]. Hypercortisolimea also decreases birth of new granule cell neurons in hippocampus which is important for memory formation. It also endangers hippocampal neurons by increasing their susceptibility to excitatory amino acids and oxidative stress. It also reduces the inhibitory influence of hippocampus on HPA axis.

Neurotropic factors regulate neural growth and differentiation and play an important role in survival and plasticity of adult neurons and glia. Elevated levels of glucocorticoids decrease the expression of CREB and therefore reduce BDNF (brain derived neurotropic factor) expression. Therefore impaired hippocampal function contributes to cognitive abnormalities of anxiety and depression [15].

Whenever a fearful situation is experienced the memory of that reaction gets stored in amygdala. If we face the same fearful situation again the memory of the past fear surfaces and the above reaction is activated. When the fear provoking event comes to an end, the amygdala resets itself to a normal level. However in certain cases the amygdala is modified and becomes fixed at more than a normal level. In such situation the fear producing stimulus is either not present or is not immediate, but in anticipation of danger, the same arousal, vigilance, physiologic preparedness, negative cognitions occur due to activation of above reaction. Such a trigger is responsible for anxiety and depression disorder [16].

This mechanism explains the co-existence of anxiety and depression

The support for this theory comes from following evidence:

1) CSF of depressed and anxious patients contain elevated levels of CRF

2) The ACTH response to exogenous CRF is blunted in patients with anxiety and depression suggesting desensitised CRF receptors secondary to cortisol hyper secretion.

3) Elevated number of CRH producing neurons in Para ventricular hypothalamic nucleus in patients with anxiety and depression.

4) It has been seen that corticosterone delivery in amygdala increases CRF mRNA in central amygdaloid nucleus and produces anxiety like behaviour [17].

5) Infusion of CRF antisense oligodeoxynucleotide into central nucleus of amygdala decreases anxiety behaviour in socially defeated rats [18].

ICD-10 Classification of Anxiety:

Phobic anxiety disorders	Agoraphobia Without panic disorder With panic disorder Social phobia Specific (isolated) phobias Other phobic anxiety disorders Phobic anxiety disorder, unspecified
Other anxiety disorders	Panic disorder (episodic paroxysmal anxiety) Generalized anxiety disorder Mixed anxiety and depressive disorder Other mixed anxiety disorders Other specified anxiety disorders Anxiety disorder, unspecified

ICD-10 Classification of Depression [19]:

Depressive episode	Mild depressive episode Moderate depressive episode Severe depressive episode without psychotic symptoms Severe depressive episode with psychotic symptoms Other depressive episodes
Atypical depression	Single episodes of "masked" depression NOS Depressive episode, unspecified
Recurrent depressive disorder	Recurrent depressive disorder, current episode mild Recurrent depressive disorder, current episode moderate Recurrent depressive disorder, current episode severe without psychotic symptoms Recurrent depressive disorder, current episode severe with psychotic symptoms Recurrent depressive disorder, currently in remission Other recurrent depressive disorders Recurrent depressive disorder, unspecified

Current Therapy: The current therapy mainly focusses on the levels of neurotransmitters in the brain. The antidepressant drugs currently in use are;

- Inhibitors of monoamine uptake which includes Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors
- Monoamine oxidase inhibitors

The current therapy for anxiety includes Benzodiazepines and Busprione. SSRIs are also used in treatment of anxiety disorders.

The need for newer therapy is increasing day by day because current medications do not provide long term solution for treatment of anxiety and depression. Also medications typically require several weeks to show clinical effect and symptoms return to normal after medication is discontinued. The patient becomes dependent on medication and the effect of medication tends to wear off quickly as patient becomes tolerant to the effects [20, 21, 22, 23].

Future advances in Treatment:

1. **CRF Receptor Antagonists**: According to the "Dysregulation of hippocampus-hypothalamic-pituitary adrenal axis (HPA Axis)" theory it is known that in response to fear the neurons in the paraventicular nucleus of hypothalamus secrete corticotrophin releasing factor (CRF) which acts on postsynaptic CRF1 receptors the activation of which is associated with symptoms of anxiety and depression. CRF is a 41 amino acid polypeptide and is responsible for mediation of behavioural, endocrine and autonomic responses to fear.

   CRF belongs to a family of structurally related peptides with members including urocortin1, urocortin2, and urocortin3. CRF acts on 2 types of receptors- CRF1 and CRF 2 both of which are G-protein coupled receptors which are encoded by 2 distinct genes.

Both the receptors are coupled to their effector mechanisms via adenylyl cylase/ cAMP second messenger system. There is one main structural variant of CRF1 which is CRF1α and three main structural variants of CRF2 namely CRF2a, CRF2b, CRF2c. CRF1 and CRF2 receptors are primarily located in choroid plexus, ventromedial hypothalamus and lateral septum.

CRF has preferential affinity for CRF1 receptors, urocortin1 shares equal affinity for both CRF1 and CRF2 receptors whereas urocortin2 and urocortin3 have preferential affinity for CRF2 receptors. The role of CRF2 receptors is more complex: CRF2 receptor activation has been associated with both enhancement as well as inhibition of stress responsivity, and other lines of evidence suggest a primary role in the suppression of feeding behaviour.

Since activation of CRF1 receptor is mainly responsible for anxiety and depressive behaviours which can be reversed by use of CRF antagonists, CRF1 receptors antagonists are being explored as primary target for development of drugs with anxiolytic and anti-depressant effects. There are no peptide agents which can effectively cross the blood brain barrier due to their high molecular weight. Moreover these are not selective towards CRF1 receptor.

Therefore, the current focus is on small molecule, non-peptide agents which can effectively cross the blood brain barrier and are selective towards CRF1 receptor. CRF1 receptor antagonists bind to a site that is a part of extracellular domain of CRF1 receptor and not on CRF binding site. Therefore, these agents act as allosteric inhibitors rather than competitive inhibitors of CRF.

CRF antagonists have demonstrated anxiolytic and antidepressant effects in several preclinical and clinical studies and are emerging as future medications for treatment of anxiety/depression [24, 25] (**table 1**).

TABLE 1: SOME OF THE CRF1 ANTAGONISTS WHICH HAVE ENTERED CLINICAL TRIALS INCLUDE [26]:

COMPANY	TITLE	DRUG	THEURAPEUTIC IMPLICATION	PHASE
GSK	A Study of the Effects of a New Antidepressant Treatment (GSK561679) in Females With Major Depressive Disorder	GSK561679 placebo	Major Depressive Disorder	Phase 2
GSK	A study to compare the Putative Anxiolytic Effect of 2 new in subjects with social anxiety disorder	GW876008, GSK561679, alprazolam	Anxiety	Phase1
GSK	A Study To Investigate Effects Of GSK561679 On Brain Activation During Emotional Processing In Healthy Volunteers	GSK561679	Depressive Disorder and Anxiety Disorders	Phase 1

Neurotrophins and Neurogenesis: An elevated level of glucocorticoids released in response to fear decrease the expression of CREB and therefore reduces BDNF (brain derived neurotropic factor) expression in hippocampus resulting in impaired hippocampal function and contributes to cognitive abnormalities of anxiety and depression. Neurotrophins are necessary for survival and growth of neurons. BDNF is most widely explored neurotrophin with antidepressant and anxiolytic effect.

It was demonstrated that hippocampal BDNF mRNA was reduced by different types of stresses. This supports the above hypothesis that low BDNF levels may contribute to atrophy and neuronal loss observed in patients with anxiety and depression. In clinical populations, serum BDNF levels have been explored as biomarkers for anxiolytic and antidepressant response. In preclinical models of depression knockout mice show reduced antidepressant response. Several potentially neurogenic compounds are being investigated as antidepressant and anxiolytic drugs. [27].

Neurotrophins bind to and cause activation of cAMP response element binding protein (CREB), a transcription factor. This causes activation of BDNF which in turn binds to tyrosine kinase B receptor. BDNF-trKB signalling pathway increases the formation and stabilization of synaptic connectivity and promotes neurogenesis [28]. Therefore agents which cause activation of CREB and promote neurogenesis in hippocampal region are being explored as potential drugs in treatment of anxiety and depression

Following table 2 gives list of drugs which have entered clinical trials [26]:

TABLE 2: DRUGS ENTERED FOR CLINICAL TRIALS

DRUG	COMPANY	THERAPEUTIC IMPLICATION	PHASE
BCI-540 Placebo	BrainCells Inc.	Treatment of Major Depressive Disorder With Concomitant Anxiety	Phase 2
Pregnenolone (nuroactive steroid)	Durham VA Medical Centre	Post-traumatic Stress Disorder (PTSD)	Phase 2
Lexapro® (escitalopram)	In Kyoon Lyoo, Seoul National University Hospital	Depression, anxiety	Phase 2

Substance P: Substance P is an 11 amino acid peptide belonging to the tachykinin family of neuro-transmitters. Tachykinin refers to a family of neuropeptides that have a common C-terminal amino acid sequence with varying N-terminal sequence and substance P like activity [29, 30]. Tachykinins found in mammals are termed as neurokinins. In addition to substance P the two other neurokinins are NeurokininA and Neurokinin B. Three classes of neurokinin receptors have been identified all of which bind to substance P to some degree. All of them are G-protein coupled receptors. These are:

1. Neurokinin1 receptor (NK1): which preferentially binds to substance P
2. Neurokinin2 receptor (NK2):which preferentially binds to neurokinin A
3. Neurokinin3 receptor (NK3): which preferentially binds to neurokininB [31, 32, 33].

The primary function of substance P is a nociceptive transmitter in afferent sensory fibres. It is released in response to noxious cutaneous stimuli and participates in conduction across sensory afferent nerves mediating pain [34, 35]. Substance P is also implicated in several physiological activities such as vomiting reflex, defensive behaviour, change in cardiovascular tone etc. [36, 37]. Recent research has shown that stimulation of amygdala in response to fear triggers the release of endogenous substance P which acts on the NK1 receptors in hypothalamus causing release of CRF from PVN neurons and leading to anxiety and depression [38, 39].

Intra-cerebral microinjection of substance P also produces symptoms resembling anxiety and depression [40]. Based on above findings it is proposed that blockade of NK1 receptors may exert antidepressant and anxiolytic effect. MK-869 (Aprepitant) is an antagonist of substance P at NK1 receptor. It has demonstrated both anxiolytic as well as anti-depressant effects in preclinical studies. Aprepitant has completed Phase III clinical trials for anxiety and depression [26].

CONCLUSION: The most important problem associated with anxiety and depression is lack of awareness about the disorder among the patients. It is estimated that less than 25% of patients affected with this disorder have access to appropriate treatments. The current drugs used in treatment of this disorder mainly focus on the levels of neurotransmitters in the brain. These are associated with many side effects. These drugs also show tolerance and dependence on prolonged usage. There is a lag time of few weeks for the drugs to exert their clinical effects.

The symptoms of disorder reappear on discontinuation of therapy. Therefore it is very essential to develop the drugs which target the HPA Axis. On-going research is focussing on HPA axis. Therefore there is urgent need for collaboration between researchers, psychiatrists and psychologists to evaluate the clinical efficacy of these potential drugs as well as increase the awareness about this disorder among the general masses.

REFERENCES:

1. Seligman MEP, Walker EF and Rodenhan DL: Abnormal Psychology. W.W. Norton & Company, Fourth Edition 2001.
2. Davison, Gerald C: Abnormal Psychology. Veronica Visentin, , 2008
3. National Institute of a Mental Health [Internet]. 2008. [Retrieved September 3 ,2008]
4. Sandra S: Depression: Questions you have- answers you need. People's Medical Society, 1997.
5. Goldberg DP, Lecrubeir Y: Form and Frequency of Mental Disorders across cultures. In: Ustin TB, Saltorius N, eds. Mental Illness in General Health Care, Chichester John Wiley and Sons, 1995:323-334.
6. Burden of Disease in India, National Commission on Macroeconomics and Health, Ministry of Health and Family Welfare, Government of India, New Delhi, September 2005.
7. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE and Wang PS: The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). Journal of the American Medical Association 2003; 23:3095-3105
8. Frederico G, Francisco S, Guimaraes, Telma GCS, De A and John FW: Role of 5-HT in stress, anxiety and depression. Pharmacology, Biochemistry and Behaviour 1996; 1:129-141
9. Siegfried K, Johan A, Sitsen JMA: Handbook of Depression and Anxiety. Marcel Dekker, Second Edition 2003.
10. Sandra EF : Recent developments in anxiety, stress and depression. Pharmacology, Biochemistry and Behaviour 1996; 1:3-12.
11. Florian H, Marcus I: Central CRH system in depression and anxiety- Evidence from clinical studies with CRH_1 receptor antagonists. European Journal of Pharmacology 2008; 583:350-357
12. Eric J, Michel B, Ralph J, Amelia J, Stephen J and Lisa M: Neurobiology of depression. Neuron 2002; 34:13-25
13. Michael D: The role of amygdala in fear and anxiety. Annual Review of Neuroscience 1992; 15:353-375
14. Patricia A, Christoph A, Annamaria C, Livia A, Carmine M: The neuro-inflammatory and neuroprogressive pathways in depression.. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2011; 35:722-729.
15. Anantha S, William T, Donald R and Tammy S: Role of stress, corticotrophin releasing factor (CRF) and amygdala plasticity in chronic anxiety. Stress 2005;4:209-219.
16. Rockville MD: Mental Health: A Report of Surgeon General. U.S Department of Health and Human Services, National Institute of Mental Health, U.S Publication Service, 1999.
17. Liebsch G, Landgraf R, Gerstberger R, Probsct JC, Wojak CT, Engelmann M, Holsboer F and Montkowski A: Chronic infusion of a CRH_1 receptor antisense oligodeoxynucleotide into central nucleus of the amygdala reduced anxiety-related behavior in socially defeated rats. Regulatory Peptides 1995; 59:229-239.
18. Jack DS, Kirk WB, Dean AM: Corticosterone delivery to the amygdala increases corticotropin- releasing factor mRNA in central amygdaloid nucleus and anxiety-like behavior. Brain Research 2000; 2:288-295.
19. ICD-10 Classification of mental and behavioral disorders, World Health Organization, Geneva, 1992.
20. Rang HP, Dale MM, Ritter JM, and Flower RJ: Rang and Dale's Pharmacology. Churchill Livingstone Elsevier, Sixth Edition 2008.
21. Tripathi KD: Essentials of Medical Pharmacology. Jaypee Brother's Medical Publishers Ltd, Sixth Edition 2010.
22. Anxiety Disorders: U.S Department of Health and Human Services, National Institute of Mental Health, U.S Publication Service NIH publication No 09 3879, 2009.

23. Depression: U.S Department of Health and Human Services, National Institute of Mental Health, U.S Publication Service, NIH publication No 11-3561, 1999.
24. John H, Cristopher K: Therapeutic utility of non-peptidic CRF_1 receptor antagonists in anxiety, depression and stress related disorders: Evidence from animal models. Pharmacology and Therapeutics 2010; 128:460-487.
25. John HK, George DM: CRF_1 receptor antagonists: treatment of stress related disorder. Drug Discovery Today: Therapeutic Strategies 2008; 161-168.
26. www.clinicaltrials.gov (last assessed on 15th October 2012).
27. Sakina JR, Sidney HK: The keys to improving depression outcomes. Neuropharmacology 2011; 21:694-702.
28. Silvia A, Fabio T, Daniela C, Critina B, Feerica C, Giacomo C, Nicholas B, Joan MCB and Nicoletta B: Trends In neuropharmacology: In memory of Erminio Costa. Neurophramacology 2011;7-8:1337-1346.
29. Ebner K, Singewald N: The role of substance P in stress and anxiety responses. Amino Acids 2006; 3:251-272.
30. Iverson L: Substance P equals pain substance?. Nature 1998; 392:334-335.
31. Radhakrishnan V, Henry JL: Electrophysiology of neuropeptides in the sensory spinal cord. Progress in Brain Research 1995; 104:175-195.
32. Vaught JL: Substance P antagonists and analgesia: a review of the hypothesis. Life Science 1988; 43:1419-1431.
33. Henry Jl: Substance P and inflammatory pain: Potential of Substance P antagonists as analgesics. Agents and Actions Supplements 1993; 41: 75-87.
34. Kerdelhue B, Gordon K, Williams R, Lenoir V, Fardin V, Chivalier P, Garret C, Duval P, Kolm P and Hodgen G: Stimulatory effect of a specific substance P antagonist (RPR 100893) of the human NK1 receptor on the estradiol-induced LH and FSH surges in the ovariectmized cynomolgus monkey. Journal of Neuroscience Research 1997; 50:94-103.
35. Stahl SM: Peptides and Psychiatry III. Substance P and serendipity: Novel psychotropics are a possibility. Journal of Clinical Psychiatry 1999; 60:140-141.
36. Sherman TG, Akil H, Watson SJ: The molecular biology of neuropeptides. Discussions in Neuroscience 1989; 6:11-58.
37. Kramer MS, Cutler N, Feighner J et al.: Distinct mechanism for antidepressant activity by blockade of central Substance P receptors. Science 1998; 281:1640-1645.
38. Cao YQ, Mantyp PW, Carlson EF, Gillespie AM, Epstein CJ and Basbaum AI: Primary afferent tachykinins are required to experience moderate to intense pain. Nature 1998; 392:390-394.
39. Rupnaik NM, Kramer MS: Discovery of anti-depressant and anti-emetic efficacy of Subsctance P receptor (NK1) antagonists. Trends in Pharmacological Sciences 1999; 20:485-490.
40. Andrew H, Markus H, Nadia MJ, Rupnaik, Thomas S and Guy G: Neuropeptide systems as novel targets for depression and anxiety disorders. Trends in Pharmacological Sciences 2003; 11:580-588.

How to cite this article:
Kaikini A, Dhande S, Patil K and Kadam V: Anxiety and Depression: Advances in Management of Disorder. *Int J Pharm Sci Res*. 2013; 4(2); 610-616.