ELSEVIER

Guidelines for the Management of Depression and Thyroid Dysfunction

An Initiative from

Endorsed by

A Clinical Practice Guideline

Guidelines for the Management of Depression and Thyroid Dysfunction

A Clinical Practice Guideline

Chairperson

Dr. R V Jayakumar, Prof of Endocrinology, AIMS, Cochin

Core committee members

- Dr. Sarita Bajaj, HOD of Medicine, MLN Medical College, Allahabad
- Dr. D Maji, HOD of Endocrinology, Vivekananda Institute of Medical Sciences, Kolkata
- Dr. K D Modi, Sr. Consultant Endocrinologist, Hyderabad
- Dr. G R Sridhar, Director-Diabetes and Endocrine Center, Vizag
- Dr. Uday Phadke, Sr. Consultant Endocrinologist, Pune
- Dr. M. Thirunavukkarasu, Prof. and HOD of Psychiatry, SRM Medical College & Research Institute, Chennai
- Dr. U C Garg, Sr. Consultant Psychiatrist, Agra
- Dr. P K Deb, Sr. Consultant Cardiologist, Kolkata
- Dr. Arup Dasbiswas, Director- Institute of Cardiovascular Sciences, IPGME & R, Kolkata
- Dr. Banshi Saboo, Director-Diacare, Ahmedabad
- Dr. Sandhya Kamath, Dean-Sion Hospital, Mumbai
- Dr. Ashok Seth, Director-Cardiology, Escort Heart Center, New Delhi

Method of development

A national task force was created, under the auspices of The Indian Thyroid Society, to review the available evidences in the field and develop evidence-based guidelines. Members of the task force included highly reputed and experienced endocrinologists and gynaecologists.

This task force worked for a period of 6 months and reviewed most evidences available on the topic. They had multiple phone conversations and a meeting to evaluate the evidence and accordingly develop recommendations. Upon completion of the guidelines, it will be reviewed and approved by all of the participants as well as the extending committee.

The committee evaluated recommendations and evidence using the methodology of the United States Preventive Service Task Force (USPSTF), on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms),is as follows (treatments or medical advice are referred to as a "service."):

Level of evidence	Description
Level A	Data derived from multiple randomized trials or meta-analyses
Level B	Data derived from a single randomized trials or large non-randomized trial
Level C	Consensus of opinion from experts or small studies, retrospective studies or registries
Level D	Data derived from Clinical experience

Class of recommendations	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established and recommendation may be considered
Class III	Evidence and/or general agreement that a given treatment or procedure is not beneficial, useful or effective and in some cases may cause harm. Not recommended

Contents

Elsevier Pharmaceutical Communications Division (South Asia)

Ajay Pratap Singh
Director

Jyotishman Boruah
Chief Coordinator and Manager Customer Relations

Dr. Pranab Sakhare
Medical Content Manager

Introduction

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairment in an individual's ability to take care of his or her everyday responsibilities.[1]

Epidemiology of Depression

Depression affects about 340 million people globally, and is the most common psychiatric disorder encountered in general practice. About one in ten patients seen in the primary care settings suffer from some form of depression.[2]

The World Health Organisation (WHO) reported that the point prevalence of unipolar depressive episodes was about 1.9% for men and 3.2% for women, and the one-year prevalence was estimated to be 5.8% for men and 9.5% for women respectively. It is estimated that by the year 2020 the burden of depression will increase to 5.7% of the total burden of diseases, if the current trends for demographic and epidemiological transition continue.[3-5]

The lifetime prevalence of depression, anxiety, and stress among adolescents and young adults around the world is currently estimated to range from 5%-70%. [6,7]

It has been seen that women are affected twice as often as men. In patients with an affected first-degree relative, the lifetime risk of depression increases by 1.5 to 3.0 times. First onset occurs most frequently in patients aged 12 to 24 years.[2,7,8]

Several Indian studies have reported prevalence rates of depression to vary from 11%-83% in primary care practices.[2,9-12]

An Indian cross-sectional study conducted by Sahoo et al found the prevalence of clinical depression in young adults to be 12.1% and that mild to extremely severe depressive symptoms were present in 18.5% of the population.[6]

The Chennai Urban Rural Epidemiological Study (CURES) was the largest population-based study to determine the prevalence of depression. This study reported an overall prevalence of depression to be 15.1%.[2]

Depression is also often observed in the elderly. The point prevalence of depressive disorders in the elderly population in India varies from [13% to 25%.13-15]

Postpartum depression (PPD) is also a very common disorder occurring in about 11%-27% of women, 6-8 weeks after childbirth.[16-18]

Sociodemographic factors that have shown to increase the risk of depression include widowed state, unemployment, low educational level, age, gender (women being more common), women with poor marital relationship or divorcee, death of a family member, personal health related events, bereavement, interpersonal and social events, financial problems, poverty and physical illnesses.[2,5,16,19-22]

Adverse Impact of Depression

Depressive disorders are the fourth highest cause of disability adjusted life years (DALYs) worldwide. It is predicted to become the second leading cause of disability in people of all ages by the year 2020. In people aged 15 to 44 years, depression is the leading cause of disability and premature death for both sexes combined.[1, 23]

The global burden of disease (GBD) 2000 study (WHO 2001) showed that depression accounts for 4.46% of total DALYs and 12.1% of total years lived with disability (YLDs) worldwide.[24-26]

Depression leads to workplace absenteeism, decreased productivity and high suicide rates, apart from disability, leading to a decline in quality of life (QoL).[27]

Herman et al assessed the QoL and economic correlates of depression and its treatment in culturally diverse primary health care settings. Patients with higher depressive symptom scores had worse health, functional status, QoL, and greater use of health services across all sites. In addition, the likelihood of treatment for depression was associated with perceptions of health, as well as severity of the depression.[28]

In a population-based study, Poongothai et al reported that about 12.4% of depressed patients had suicidal thoughts.[2]

In another study, Reddy et al reported that about 50% of the individuals who have committed suicide, had a primary diagnosis of depression.[24]

In their study, Srivastava et al assessed the prevalence of suicidal ideation and attempt in patients with major depressive disorder. The incidence of suicidal attempt was 16.6% in patients with a major depressive episode and suicidal ideation. Statistically, a higher risk of suicidal attempt was found in individuals <30 years of age. Intensity of suicidal thoughts, agitation and paranoid symptoms were more in attempters, whereas general somatic symptoms and

hypochondriasis were more in non-attempters. Young patients with depression, especially unmarried men, housewives, students and those with class 10 or higher education, having severe suicidal ideation with agitation or paranoid symptoms were more prone to attempt suicide.[29]

Painuly et al explored some of the antecedents, concomitants, and consequences of anger attacks in patients with depression. Depressed patients with anger attacks exhibited more suicide-related phenomena and dysfunction scores in comparison to depressed patients without anger attacks. Depressed patients with anger attacks also had higher scores of anxiety, irritability, trait-anger, anger-out, anger expression, psychoticism, hassles, and poor quality of life.[30]

Depressive disorders are more common in patients with physical illness than in those without. MacHale et al found that one-third of medical in-patients reported mild to moderate symptoms of depression. Depression pre-dates the medical illness in up to 25% of patients with comorbid depression, and is associated with an increase in somatic complaints.[31]

Hays et al conducted a 2-year observational study to evaluate the change in functional status and well-being in adult outpatients with depression compared to patients with chronic general medical illnesses. The study reported that depressed patients have substantial and long-lasting decrements in multiple domains of functioning and well-being that equal or exceed those of patients with chronic medical illnesses.[32]

Studies of community and clinic-based samples indicate that physical illness is often comorbid with mental illness, especially among elderly persons. Gierz et al found that 90% of the depressed elderly patients receiving outpatient psychiatric treatment had at least one concurrent physical illness and 63% had more than one.[33]

Proctor et al reported that almost three-fourths of depressed elderly patients had at least one comorbid condition requiring first-line treatment; nearly half had two, and one-fourth had three or more. Comorbid physical illness and cognitive impairment was significantly and negatively associated with elderly patients' functional impairment at discharge. Depressed patients with higher medical comorbidity had significantly more needs for services after they left acute care.[34]

The commonly reported physical illnesses in patients with depression in various clinical studies include; cardiovascular (hypertension, coronary artery disease, ischaemic heart disease), thyroid disease (hypothyroidism

and hyperthyroidism), diabetes mellitus, osteoarthritis, cataract, age related macular degeneration, end stage renal disease, obsessive compulsive disorder, epilepsy, medical inpatients, cancer etc.[24,35-47]

Depression is a strong independent risk factor for ischemic heart disease. Regardless of cardiac status and history, depressed patients exhibit significant alterations in platelet physiology that may increase risk for thrombus formation. van den Brink et al reported that depression frequently remains undiagnosed and untreated in patients with cardiovascular disease (75% depression diagnosis missed), and only half of the 25% correctly diagnosed are ultimately treated for comorbid depression.[48,49]

Depression has a negative prognostic effect on mortality when it develops following an acute myocardial infarction (MI). As many as 65% of patients report symptoms of depression following an acute MI, with 15% to 22% developing major depressive disorder.[49]

In post–myocardial infarction patients, there is a fourfold to six fold increase in mortality rate among those suffering from depression.[50]

Patients with cancer and co-morbid depression are also at higher risk of death and at higher risk of longer hospital stays.[51,52]

Studies revealed high anxiety and depression scores as well as higher psychological distress in patients diagnosed with cancer.[53,54]

Recommendations

- Prevalence of depression is high in the society especially among women (IIa/B).
- Severe depression usually has more adverse outcomes in younger patients (IIb/C).
- Depression is associated with a very high rate of morbidity (IIa/B).
- Depression is present as co-morbidity with many existing medical illnesses including thyroid dysfunction (IIa/B).

Relation Between Thyroid Dysfunction and Depression

Comorbid depression is associated with increased medical symptom burden, functional impairment, medical costs, poor adherence to self-care regimens and increased risk of morbidity and mortality, especially in patients with chronic medical disorders. Depression may worsen the course of medical disorders because of its effect on proinflammatory factors, hypothalamic-pituitary axis, autonomic nervous system, and metabolic factors, in addition to being associated with a high risk of obesity, sedentary lifestyle, smoking and poor adherence to medical regimens.[55]

There has long been an interest in the relation between thyroid function and the course of a depressive episode. As part of that interest, many studies have evaluated both the predictive value of baseline thyroid indices and subsequent response to antidepressant treatment, as well as the change in these indices with treatment. [56-58]

Hyperthyroid patients frequently report anxiety along with emotional lability, impatience and irritability, restlessness, overactivity, distractible and problems with sleep and appetite. These symptoms are very much similar to those seen in depressed patients.[59-62]

On the other hand patients with hypothyroidism can show progressive loss of interest and initiative, slowing of mental processes, poor memory for recent events, fading of the personality's color and vivacity, general intellectual deterioration, depression with a paranoid flavor, and eventually, if not checked, to dementia and permanent harmful effects on the brain.[60,63]

Moreover, hypothyroidism is significantly associated with refractory depression, suggesting that this characterizes one biological subtype of refractory depression.[64,65]

Autoimmune thyroiditis is found in nearly 15% of depressed patients with exaggerated response to the TRH stimulation test or hypothyroidism.[66,67]

Fountoulakis et al suggested that depression often co-exists with autoimmune subclinical thyroiditis and hence depression may cause alterations in the immune system, or that in fact it could be an autoimmune disorder itself.[68]

Depressed patients, although viewed as biochemically euthyroid, have alterations in the function of hypothalamic-pituitary-thyroid axis. Up to 10% of individuals with depression may present with elevated levels of thyroid-stimulating

hormone (TSH) and normal thyroxine (T4) and triiodothyronine (T3) levels. The clinical impact of an elevated TSH level is still unclear, but preliminary evidence suggests that it may predict a poor response to antidepressants.[56-58]

In other cases, there may be slight elevation of the serum thyroxine (T4), loss of the nocturnal TSH rise, blunted thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) stimulation and predisposition to autoimmune thyroiditis. [57,58]

One explanatory hypothesis for the mechanism of T4 increase in depression is based on the increase of cortisol (hypercortisolism of depression), believed to lead to an activation of the hypothalamic neurons which produce the thyrotropin releasing hormone (TRH) and, consequently, of the thyroid function. Depression has also been found to cause an inhibition in the 5'-deiodinase type II (D-II) enzyme, probably due to the increase in cortisol levels. This enzyme is responsible for the transformation of T4 to T3 in the brain, and, consequently, its inhibition triggers the conversion of T4 by other enzyme, type III brain 5'-deiodinase (D-III), therefore producing rT3, which blocks thyroid effect and is an indicator of reduced transport of T4 into the cell.[66,69]

Hypothyroid, hyperthyroid and depressed patients share a number of clinical features in common. Some research workers use the "brain hypothyroidism" hypothesis to explain the pathogenesis of depression. They suggest that depression is a state of local hypothyroidism in brain with normal peripheral thyroid hormone concentrations as a result of brain type II deiodinase inhibition and impaired transport of T4 across the blood brain barrier. This theory seems to be compatible with the serotonin deficiency hypothesis of depression. Some studies confirm the existence of classical feedback between serotoninergic and hypothalamus-pituitary-thyroid systems. TRH remains under a constant inhibition by serotonin and reduced intracerebral serotonin concentration seen in depression will lead to increased TRH concentration in the brain tissue. This mechanism is probably responsible for blunted TSH response to TRH stimulation.[57,58]

A blunted TSH response may be seen in 25% 30% of patients with unipolar major depression due to hypersecretion of hypothalamic TRH, hypercortisolemia and transient hyperthyroxinemia.[70,73]

Whereas, nearly 10% to 40% of depressed subjects showed an exaggerated response to the TRH stimulation test.[66,71,74]

Thus an exaggerated TSH response to TRH is seen in depressed patients with hypothyroidism and blunted TSH response to TRH is seen in depressed patients with hyperthyroidism.[66,75]

Kirkegaard et al found that the concentration of free T4 and free reverse T3 (rT3) in the cerebrospinal fluid (CSF) was relatively increased during depression, but reduced when the clinical recovery occurs, probably reflecting an increased supply of T4 from the serum and an increased production of rT3 from T4 in the brain. This leads to the idea that depression is associated with a relative hyperthyroid state and that the decrease of brain T4 is needed for an adequate antidepressive response.[66,76]

Recommendations

- Depressed patients have definite alterations in the function of hypothalamic-pituitary-thyroid axis and it may be seen with both hypo- and hyperthyroidism (IIa/B).
- An exaggerated TSH response to TRH is seen in depressed patients with hypothyroidism and blunted TSH response to TRH is seen in depressed patients with hyperthyroidism (IIb/C).

Depression in Patients with Thyroid Dysfunction

Patients with overt hypothyroidism can develop psychiatric symptoms similar to that seen in depression.[77-79]

Psychiatric disorders such as psychotic disorders, depressive disorders, and rapid cycling bipolar disorder may be seen in hypothyroidism.[80]

Prevalence of depressive symptoms is close to 50% in people with hypothyroidism and about 28% with hyperthyroidism.[66,81]

In another study, Demartini et al found that 63.5% of patients affected by subclinical hypothyroidism (SCH) had depressive symptoms.[47]

Haggerty et al assessed the lifetime history of major depression in subjects with SCH. They found that the lifetime frequency of depression was significantly higher in the subjects who met the criteria for SCH (56%) than in those who did not (20%), suggesting that SCH may lower the threshold for the occurrence of depression.[59,82]

Fava et al studied the prevalence of thyroid abnormalities among depressed outpatients. They found no clinically overt cases of hyperthyroidism or hypothyroidism. Of the patients examined, 2.6% had slightly elevated TSH levels and, subnormal levels of T4 or fT4I were found in <1% of patients. They concluded that in patients with depression, hypothyroidism and hyperthyroidism is not common.[83]

The prevalence of depressive disorder in patients with thyrotoxicosis has been reported to be about 31-69%, and the prevalence of anxiety disorders as 33-61%.[80,84-86]

Suwalska et al evaluated the impact of thyroid dysfunction on the quality of life (QoL) of hyperthyroid patients and assessed the frequency and severity of depressive symptoms occurring in this group of patients. Depressive symptoms were frequent in hyperthyroidism, occurring in 40% of the hyperthyroid patients. Hyperthyroid patients presented with significantly decreased perception of quality of life and health state, and scored worse in physical domain and global score of WHO QoL.[87]

Similar findings were reported by Bunevicius et al.[88]

Rockel et al observed a significant increase in anxiety, a sense of not feeling

well and emotional irritability as well as a tendency towards depressiveness, and an increased lack of vitality and activity in hyperthyroid patients compared to healthy controls.[89]

Bommer et al investigated the psychopathological and neuropsychological symptoms in patients with subclinical and remitted hyperthyroidism. Forty-three percent of patients (10% of controls) complained of "seriously reduced" well-being with feelings of fear, hostility, and inability to concentrate. While a fearful-agitated syndrome dominated in the initial phase of the illness, a mainly depressive syndrome was characteristic after a longer period of remission. More than 25% of the patients (2% of controls) showed "markedly impaired" neuropsychological functioning. Patients with a relapse within 2.5 years exhibited the most abnormal results. Even after a longer period of hormonal remission, there was no complete psychopathological and neuropsychological normalization.[90]

Total T4 levels or TT4/TBG ratios may play a crucial role in the development of the predominantly nervous symptoms in subclinical hyperthyroidism.[91]

Schlote et al reported that depressive symptoms in patients with subclinical hyperthyroidism probably results from the central changes which lead to attenuated TSH responses to TRH, or from elevated but still normal thyroxine levels, which possibly enhance the effect of catecholamines.[92]

Lee et al assessed the association of hyperthyroidism by the Hamilton Rating Scale for Anxiety (HAM-A) indicating anxiety, and the Zung Self-Rating Depression Scale (Zung Scale) indicating depression. They found that anxiety and depression were more severe in patients with hyperthyroidism than in those with normal thyroid function.[93]

Sonino et al reported that depression occurs in 23% of patients with Graves' disease and it appears in the prodromal phase in 14% of such patients.[94]

Recommendations

The prevalence of depression is common in patients with hypo- as well as hyperthyroidism (IIa/B).

Thyroid Dysfunction in Patients with Depression

It is reported that most patients with depression may have alterations in their thyroid function.[58]

Studies have shown that depressed patients may have an altered thyroid-stimulating hormone response to thyrotropin-releasing hormone (TRH), an abnormally high rate of antithyroid antibodies and elevated cerebrospinal fluid (CSF) TRH concentrations.[67]

Rao et al measured the serum thyroid hormone levels in psychiatric patients with depression. Basal serum triiodothyronine and serum thyroxine was lower in female patients with major depression than in healthy women. In female patients, 45% with major depression, 25% with anxiety disorder and 35% with anxious depression showed a blunted TSH response.[95]

It has been found that a significant proportion of patients with depression have early hypothyroidism. Hypothyroidism might be associated with anxiety or refractory depression.[67,96]

The prevalence of clinical hypothyroidism in psychiatric patients ranges from 0.5% to 8%, but various other studies have shown different results based on the population studied.[66,81,97] (2004), pp. 40–48 (in Portuguese).

Gold et al evaluated the relationship between hypothyroidism and depression. They found that 8% of patients had some degree of hypothyroidism. About 1% had overt hypothyroidism, 4% had SCH and 3.6% had mild hypothyroidism.[98]

According to Gupta et al, the overall prevalence of hypothyroidism in major depressive disorder was estimated as [20.5%.99]

The significance of SCH for psychiatric disorders, particularly affective illness, is not clear. Joffe et al found that about 13% of patients with major depression had evidence of SCH. With regard to clinical features, the frequency of individual depressive symptoms was similar in those with and without SCH; however, concurrent panic disorder was more common in those without SCH.[100]

Oppedal et al found that approximately 8% of depressed patients had SCH compared to only 5% of the general population.[101]

Sintzel et al, in a metaanalysis, reported that subclinical hypothyroidism

was present in 52% of patients with resistant depression, against 8-17% in patients with simple depression and 5% in the overall population. Moreover, antithyroid antibody levels (group IV hypothyroidism) were significantly higher in refractory depressed patients (9-20% against 7% in patients with simple depression and 5% in the overall population).[102]

Howland et al reviewed thyroid dysfunction in patients with refractory depression. They found that in six clinical studies, 52% of patients with refractory depression had evidence of SCH.[64]

Several investigations have suggested that subclinical autoimmune hypothyroidism may represent a risk factor for the development of affective disorders.[103,104]

Moreover, recent evidence seems to indicate that high levels of thyroid antibodies in depressive disorders are at increased risk of major depressive disorder (MDD) and panic disorder (PD) in patients with thyroid disease.[105-107]

Studies have shown an increased prevalence of affective disorders in patients with celiac disease and interestingly, the prevalence of autoimmune thyroid diseases has been found to be high in celiac patients.[108-110]

Nemeroff et al assessed the presence of antithyroid (antimicrosomal and antithyroglobulin) antibodies in psychiatric patients with prominent depressive symptoms. They found that 20% of patients had detectable titers of antithyroid antibodies. All patients with symptomless autoimmune thyroiditis had normal baseline serum thyrotropin concentrations and normal thyroid function (as assessed by T4, T3 uptake, and free thyroxine index). These findings support the hypothesis of subtle thyroid dysfunction in psychiatric patients with prominent depressive symptoms.[111]

Haggerty et al determined the frequency of antithyroglobulin and antimicrosomal antibodies in patients admitted to the psychiatric ward. They found that patients with depression had a higher rate of positive antithyroid antibody titers than other patients.[112]

Hickie et al investigated the relationship between hypothyroidism and treatment-resistant depression (TRD) in patients with chronic depressive disorder. They found that 22% of patients with TRD had evidence of clinical or SCH which was not accounted for by differences in age or prior exposure to lithium and/or carbamazepine. This study suggests that relative hypothyroidism may play a role in the development of some treatment-resistant depressive disorders.[65]

These findings indicate that hypothyroidism is significantly associated with refractory depression.[64]

Demet et al determined symptomatology of depression and anxiety in hyperthyroid and euthyroid patients. Depression and anxiety were the most frequent diagnosis in hyperthyroid patients. The study concluded that hyperthyroidism and syndromal depression–anxiety have overlapping features that can cause misdiagnosis during acute phase. In addition to specific symptoms of hyperthyroidism, psychomotor retardation, guilt, muscle pain, energy loss, and fatigue seem to appear more frequently in patients with comorbid depression and hyperthyroidism; thus presence of these symptoms should be a warning sign to nonpsychiatric professionals for the need of psychiatric consultation.[59]

Orenstein et al noted a 13% prevalence of hyperthyroidism among patients who had a history of depression/panic/agoraphobia.[113]

In another study Lesser et al found the prevalence to be 11%.[96,114]

Thyroid hormone is essential for the growth and maturation of many target tissues, including the brain and skeleton. As a result, abnormalities of thyroid gland function in infancy and childhood result not only in the metabolic consequences of thyroid dysfunction seen in adult patients, but also behavioral disturbances due to shortened attention span, and emotional lability.[115]

Bongers-Schokking JJ et al found that initial and postinitial suboptimal treatment of congenital hypothyroidism (CH) leads to abnormalities in IQ and specific fields. Overtreatment may advance cognitive development in children, whereas suboptimal initial treatment may lead to behavioral problems. Hence, they recommended that TSH concentrations be maintained within the normal range in patients with CH.[116]

A similar finding was seen by Roy et al who found that children with severe CH treated early with a high dose of levothyroxine have normal global development and behavior at school entry.[117]

Recommendations

- Subclinical autoimmune hypothyroidism is a risk factor for the development of affective disorders (IIb/C).
- Both hypothyroidism and hyperthyroidism are seen in psychiatric disturbances (IIa/B).
- Hyperthyroidism and depression have overlapping features that can cause misdiagnosis during acute phase (IIa/B).
- In children behavioural disturbances may be associated with thyroid dysfunction (IIa/B).
- Hypothyroidism may be associated with refractory depression (IIa/B).

Postpartum Depression and Thyroid Disease

Thyroid dysfunction is often accompanied by mood disturbances. Postpartum thyroid dysfunction (PPTD) and postpartum depression (PPD) occur frequently; the peak incidence of both conditions occurs at about two to five months postpartum.[118]

Lucas et al evaluated the relation between the presence of PPTD and PPD and reported an incidence rate of depression of 1.7% in women with thyroid disease postpartum.[119]

Bunevicius et al assessed 199 pregnant women three times during pregnancy for depressive disorder and for TSH and FT4 concentrations. Prevalence of depressive disorder was 6.5% in early pregnancy, 3.0% in mid trimester of pregnancy and 3.5% in last trimester of pregnancy. There were no women with overt thyroid dysfunction. Subclinical hyperthyroidism was found in 23% of women in early pregnancy, in 5% of women in the middle of pregnancy and in 6% of women in later part of pregnancy. In late pregnancy, depressed women compared to non-depressed women had significantly higher FT4 concentrations and a strong trend towards lower TSH concentrations as well as higher prevalence of SCH. These findings show an association between thyroid dysfunction and depression in later part of pregnancy.[120]

Harris et al assessed the psychiatric status in 145 thyroid antibody positive and 229 thyroid antibody negative women postpartum. About 43% antibody positive women and 28% antibody negative women had mental ill health 6 weeks after delivery. On follow up, antibody positive women (47%) showed significantly greater depression than antibody negative women (32%) regardless of thyroid dysfunction. Antibody positive women showed higher mean scores for depression on different scales. The authors concluded that depressive symptoms are associated with positive thyroid antibody status in the postpartum period.[121]

Because of the potential association between PPD and PPTD, and because hypothyroidism is a reversible cause of depression, women with PPD should also be assessed for hypothyroidism.[122.123]

The rationale behind a possible association between positive PPD and postpartum thyroiditis is that hypothyroidism is associated with depression outside of the postpartum period and that hypothyroidism appears to decrease 5-hydroxytrytamine neurotransmission, which reverses with thyroid hormone replacement. Although the pathophysiological evidence between the association of

thyroid antibodies and depression is less clear; it is speculated that cytokines released during thyroid autoimmune reactions, such as IL-1 and IL-6, may interact with central neurotransmission, thereby initiating depression.[123]

Kuijpens et al investigated whether the presence of thyroperoxidase antibodies (TPOAbs) during pregnancy can be regarded as a marker for depression in the first year postpartum, particularly in relation to (overt or subclinical) thyroid dysfunction and other determinants of depression. About 14.1% of the pregnant women had TPOAbs at one or more time points, and 40.1% had depression at one or more time points postpartum. TPOAbs were independently associated with depression at 12 weeks gestation and at 4 and 12 weeks postpartum. After the exclusion of women who were depressed at 12 weeks gestation, the presence of TPOAbs during early pregnancy was still found to be associated with the development of PPD; while after exclusion of women who had depression in earlier life, TPOAb during early gestation was still associated with PPD. The presence of TPOAbs during gestation is associated with the occurrence of subsequent depression during the postpartum period and as such can be regarded as a marker for depression.[124]

Similar findings were reported by Breese McCoy et al.[125]

In another study, Pop et al found a significant relation between the occurrence of depression and thyroid dysfunction. Moreover, depressed mood was related to the course of the thyroid dysfunction. Thyroid dysfunction also occurred more often in women with depression than women without depression.[118]

Postpartum thyroiditis is a destructive thyroiditis induced by an autoimmune mechanism. Approximately 20%-30% of women with postpartum thyroiditis have the characteristic sequence of hyperthyroidism, which usually begins 1-4 months after delivery and lasts for 2-8 weeks. This is followed by hypothyroidism, which also lasts from about two weeks to six months, and then recovery occurs. The symptoms of hypothyroidism are usually mild. However, 20%-40% have only hyperthyroidism and the remaining 40%-50% have only hypothyroidism, which begins two to six months after delivery and lasts for up to 1 year.

In most women thyroid function returns to normal within 12-18 months of the onset of symptoms. However, approximately 20% of those who go into a hypothyroid phase will remain hypothyroid.122,126,127

Recommendation

- Postpartum thyroid dysfunction and postpartum depression occur frequently (IIa/B).
- The presence of TPOAbs during gestation is a marker for the occurrence of subsequent depression during the postpartum period (IIb/C).

Treatment of Thyroid Dysfunction in Patients with Depression

Several studies have shown the beneficial effect of treating patients with depression.

Berndt et al showed that the level of perceived at-work performance is negatively related to the severity of the depressive illness and that a reduction in the severity of depression rapidly improves the patient's work performance in chronically depressed individuals.[128]

Studies of the effect of depression on work disability and health care costs show greater disability and higher costs among depressed patients and that improvement in depression is associated with reduced disability and lower costs.[129,130]

Fountoulakis et al suggested that as thyroid dysfunction and depression coexist, it is important to identify thyroid dysfunction and treat it early with thyroid replacement therapy.[67]

Thyroid hormones have been used as accelerators and augmenters of antidepressant response. The use of thyroid hormones to supplement antidepressants is based on evidence supporting a bidirectional connection between thyroid function and depression. In the event that thyroid replacement therapy is considered for augmentation in cases of resistant depression, one could either opt for T4 or T3. T3 may be a more effective antidepressant, but is not routinely used for thyroid replacement. On the other hand, less evidence is available to support the use of thyroxine (T4).[131,132]

Baumgartner A et al reviewed 8 open clinical trials conducted by 7 different study groups and demonstrated that augmentation with thyroxine (T_4) had antidepressant and prophylactic effects in roughly 50% of patients completely resistant to all other antidepressant and prophylactic therapies. Beneficial effects were observed in unipolar and bipolar (rapid-cycling and non-rapid-cycling) patients, but only when an antidepressant or prophylactic drug was administered concomitantly.[133]

Further trials are needed to specify the role of thyroid replacement therapy in augmenting response to antidepressant therapy in resistant cases.

Monzani et al assessed the effects of levothyroxine (LT4) treatment on selected neuropsychological and behavioral features by means of standardized

tests in patients with SCH. They found that after LT4 treatment, the patient's performances showed an improvement in memory skills, somatic complaints and obsessionality ratings.[79]

Sawka et al determined whether hypothyroid individuals with depressive symptoms experience an improved mood and/or sense of well-being when euthyroidism is maintained with a combination of T3 and LT4 compared with LT4 therapy alone. They concluded that the current data do not support the routine use of T3 in addition to LT4 to maintain euthyroidism in hypothyroid patients who are receiving stable doses of LT4 hormone, but who complain of depressive symptoms. Moreover, the long-term safety of combining T3 with LT4 therapy is unknown and large, multicenter, blinded, randomized, controlled trials would be required to support changing the current approach.[134]

Currently there is no consensus for combining T3 with LT4. Rack et al reported that depression may be more responsive to a replacement regimen that includes T3 rather than LT4 alone in hypothyroid patients thus warranting inclusion of T3 in the treatment regimen after adequate trial with T4 alone. Moreover the authors also suggest that depressed patients should be screened for hypothyroidism.[135]

Bunevicius et al found that in patients with hypothyroidism, partial substitution of T3 for LT4 improves mood and neuropsychological function.[136]

Altshuler et al performed a meta-analysis on the use of thyroid hormone supplementation to accelerate the treatment of depression and to determine whether there is sufficient evidence to support the clinical efficacy of this strategy. They found that this meta-analysis supported the efficacy of T3 in accelerating clinical response to tricyclic antidepressants in patients with nonrefractory depression. Furthermore, women benefited more than men from this intervention.[137]

Treatment of postpartum thyroiditis and depression

Majority of women in the hyperthyroid phase of PPTD usually do not require intervention as it is mild and rarely lasts more than a couple of months. However, thyroid function (TSH, free T4, and T3) should be monitored every 4-8 weeks to confirm resolution of biochemical abnormalities or to detect the development of more severe hypothyroidism, indicating possible permanent hypothyroidism. Symptomatic cases are managed with a short course of beta-blockers titrated based on symptom severity. It is controversial whether to treat women in the hypothyroid phase of PPTD. Women with a TSH of 4-10 mIU/L

and who are asymptomatic require no treatment. Women with a TSH of >10 mIU/L and those who are symptomatic with a TSH between 4 and 10 mIU/L should be treated with LT4 50 to 75µg/day and 25 to 50µg/day respectively. Asymptomatic women with a TSH between 4 and 10 mIU/L and planning a subsequent pregnancy in the near future also require therapy. However, about 30% of women never recover from the initial hypothyroid phase, and a rising TSH level is indicative of persistent hypothyroidism, requiring long-term LT4 therapy. The duration of therapy with LT4 is controversial. Either attempt to discontinue treatment approximately 1 year postpartum following the occurrence of PPT, or maintain therapy until the woman completes her family, and begin a weaning trial of LT4 one year after the birth of the final child.[122,123,138]

However, whether or not LT4 therapy alters the incidence or severity of the depression associated with postpartum thyroiditis is controversial.[139,140]

Harris et al conducted a randomized double-blind placebo-controlled trial to investigate the hypothesis that stabilizing thyroid function postpartum would reduce the occurrence and severity of PPD. Levothyroxine therapy (100 µg/d) was administered to thyroid-antibody-positive women from 6 weeks to 6 months postpartum, assessing their psychiatric and thyroid status at 4-weekly intervals. There was no evidence that LT4 had any effect on the occurrence of depression. They concluded that the excess of depression in thyroid-antibody-positive women in the postpartum period is not corrected by daily administration of thyroxine.[140]

Recommendations

All patients with depression should be screened for hypothyroidism (IIa/B).

Women with postpartum thyroiditis usually do not require intervention as it is mostly mild and temporary. Symptomatic cases are managed with a short course of beta-blockers. Women with a TSH of 4-10 mIU/L and who are asymptomatic require no treatment. Women with a TSH of >10 mIU/L and those who are symptomatic with a TSH between 4 and 10 mIU/L should be treated with LT4 50 to 75µg/day and 25 to 50µg/day respectively. Asymptomatic women with a TSH between 4 and 10 mIU/L and planning pregnancy should also be treated (IIa/B).

Screening

There is little doubt that thyroid hormone plays a major role in the regulation of mood, cognition and behavior. Clinical studies have shown that hypothyroid patients have a more severe form of depression and a slower or impaired response to antidepressant therapy. Hence, patients with thyroid dysfunction frequently experience a variety of neuropsychiatry sequele. The frequency of misdiagnosis and mistreatment, and the potential for poor prognosis, point to the importance of a high degree of suspicion of thyroid dysfunction and the need for thyroid screening in all psychiatric patients.[141,142]

It is necessary to perform thyroid function tests to make differential diagnosis of anxiety and depressive disorders.[59]

Hence, screening for thyroid function tests should be an integral part of the assessment of adults presenting with a depressive episode.[143]

Almeida et al found that the odds of prevalent depression were 0.8 for men with SCH and 1.4 for those with subclinical hyperthyroidism. The hazard ratio of incident depression associated with SCH was 0.7. They found that subclinical thyroid disease was not associated with prevalent or incident depression in older men and hence routine screening of subclinical thyroid dysfunction among older adults with depression is not justified.[144]

In another study, Kim et al found that hyperthyroidism, but not hypothyroidism was associated with cognitive impairment and there was no evidence for an association of either with depression in patients aged ≥65 years.[145]

A similar finding was seen by Roberts et al in elderly patients (≥65 years).[146]

Andrade et al suggested that due to the high prevalence of hypothyroidism and depression observed in clinical practice, depressive symptoms must be considered in patients with thyroid dysfunction and depressed patients should be tested for TSH.[147]

Both mood disorders and thyroid dysfunction are common in pregnancy and the postpartum period and have significant implications in both mother and child. It is now widely recognized that disturbances of mood and cognition often emerge in association with putative disturbance of thyroid metabolism in the brain. Several small studies have shown the associations between clinical and subclinical thyroid dysfunction and depression during pregnancy or the postpartum period.[148]

Women who develop PPTD should be screened for presence of postpartum thyroiditis. Screening should include an antithyroid peroxidase antibody titer and TSH level.[123,149]

Recommendation

Patients with thyroid dysfunction frequently experience a variety of neuropsychiatry sequele. Due to the similarity in presenting symptoms there is a high frequency of misdiagnosis and mistreatment, hence there is a need for thyroid screening in all psychiatric and patients with mood disturbances (IIa/B).

Screening for thyroid dysfunction in patients with depression should be done with TPO & TSH (IIa/C).

Women with mood disturbances during pregnancy should be screened for thyroid dysfunction (IIb/C).

Women who develop postpartum depression should be screened for presence of postpartum thyroiditis (IIa/B).

Summary

Introduction

Recommendations

- Prevalence of depression is high in the society especially women (IIa/B).
- Severe depression usually has more adverse outcomes in younger patients (IIb/C).
- Depression is associated with a very high rate of morbidity (IIa/B).
- Depression is present as co-morbidity with many existing medical illnesses including thyroid dysfunction (IIa/B).

Relation Between Thyroid Dysfunction and Depression

Recommendations

- Depressed patients have definite alterations in the function of hypothalamic-pituitary-thyroid axis and it may be seen with both hypo- and hyperthyroidism (IIa/B).
- An exaggerated TSH response to TRH is seen in depressed patients with hypothyroidism and blunted TSH response to TRH in depressed patients with hyperthyroidism (IIb/C).

Depression in Patients with Thyroid Dysfunction

Recommendations

- The prevalence of depression is common in patients with hypo- as well as hyperthyroidism (IIa/B).

Thyroid Dysfunction in Patients with Depression

Recommendations

- Subclinical autoimmune hypothyroidism is a risk factor for the development of affective disorders (IIb/C).
- Both hypothyroidism and hyperthyroidism are seen in psychiatric disturbances (IIa/B).
- Hyperthyroidism and depression have overlapping features that can cause misdiagnosis during acute phase (IIa/B).

- In children behavioral disturbances may be associated with thyroid dysfunction (IIa/B).
- Hypothyroidism may be associated with refractory depression (IIa/B).

Postpartum Depression and Thyroid Disease

Recommendation

- Postpartum thyroid dysfunction and postpartum depression occur frequently (IIa/B).
- The presence of TPOAbs during gestation is a marker for the occurrence of subsequent depression during the postpartum period (IIb/C).

Treatment of Thyroid Dysfunction in Patients with Depression

Recommendations

- All patients with depression should be screened for hypothyroidism (IIa/B).
- Women with postpartum thyroiditis usually do not require intervention as it is mostly mild and temporary. Symptomatic cases are managed with a short course of beta-blockers. Women with a TSH of 4-10 mIU/L and who are asymptomatic require no treatment. Women with a TSH of >10 mIU/L and those who are symptomatic with a TSH between 4 and 10 mIU/L should be treated with LT4 50 to 75µg/day and 25 to 50µg/day respectively. Asymptomatic women with a TSH between 4 and 10 mIU/L and planning pregnancy should also be treated (IIa/B).

Screening

Recommendation

- Patients with thyroid dysfunction frequently experience a variety of neuropsychiatry sequele. Due to the similarity in presenting symptoms there is a high frequency of misdiagnosis and mistreatment, hence there is a need for thyroid screening in all psychiatric and patients with mood disturbances (IIa/B).
- Screening for thyroid dysfunction in patients with depression should be done with TPO & TSH (IIa/C).
- Women with mood disturbances during pregnancy should be screened for thyroid dysfunction (IIb/C).
- Women who develop postpartum depression should be screened for presence of postpartum thyroiditis (IIa/B).

References

1. Depression. WHO. Available from: http://www.who.int/mental_health/management/depression/definition/en/index.html (Accessed on November 2011).
2. Poongothai S, Pradeepa R, Ganesan A, Mohan V. Prevalence of Depression in a Large Urban South Indian Population — The Chennai Urban Rural Epidemiology Study (Cures – 70). *PLoS One.* 2009; Vol. 4 (9):e7185.
3. Rugulies R, Bültmann U, Aust B, Burr H. Psychosocial Work Environment and Incidence of Severe Depressive Symptoms: Prospective Findings from a 5-Year Follow-up of the Danish Work Environment Cohort Study. *Am J Epidemiol.* 2006; Vol. 163 (10):877–887.
4. Gururaj G, Girish N, Isaac MK. Mental, neurological and substance abuse disorders: Strategies towards a systems approach. NCMH Background Papers-Burden of Disease in India. Pages: 226-50.
5. Grover S, Dutt A, Avasthi A. An overview of Indian research in depression. *Indian J Psychiatry*. 2010; Vol. 52 (Suppl 1):S178-S188.
6. Sahoo S, Khess CR. Prevalence of depression, anxiety, and stress among young male adults in India: a dimensional and categorical diagnosis-based study. J Nerv Ment Dis. 2010; Vol. 198 (12):901-904.
7. Remick RA. Diagnosis and management of depression in primary care: a clinical update and review. MAJ. 2002; Vol. 167 (11):1253–1260.
8. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA. 1996; Vol. 276 (4):293-299.
9. Nandi DN, Banerjee G, Mukherjee SP, Ghosh A, Nandi PS, Nandi S. Psychiatric morbidity of a rural Indian community changes over a 20 year interval. Br J Psychiatry. 2000; Vol. 176:351-356.
10. Madhav MS. Epidemiological Study of Prevalence of Mental Disorders in India. Indian J Community Med. 2001; Vol. 26 (4):198-200.
11. Amin G, Shah S, Vankar GK. The prevalence and recognition of depression in primary care. Indian J Psychiatry. 1998; Vol. 40 (4):364-369.
12. Pothen M, Kuruvilla A, Philip K, Joseph A, Jacob KS. Common mental disorders among primary care attenders in Vellore, South India: Nature, prevalence and risk factors. Int J Soc Psychiatry. 2003; Vol. 49 (2):119-125.
13. Taqui AM, Itrat A, Qidwai W, Qadri Z. Depression in the elderly: Does family system play a role? A cross-sectional study. BMC Psychiatry. 2007; Vol. 7:57.
14. Prakash O, Gupta LN, Singh VB, Singhal AK, Verma KK. Profile of psychiatric disorders and life events in medically ill elderly: experiences from geriatric clinic in Northern India. Int J Geriatr Psychiatry. 2007; Vol. 22 (11):1101-1105.
15. Barua A, Kar N. Screening for depression in elderly Indian population. Indian J Psychiatry. 2010; Vol. 52 (2):150-153.
16. Patel V, Rodrigues M, DeSouza N. Gender. Poverty, and Postnatal Depression: A Study of Mothers in Goa, India. Am J Psychiatry. 2002; Vol. 159 (1):43-47.
17. Chandran M, Tharyan P, Muliyil J, Abraham S. Post-partum depression in a cohort of women from a rural area of Tamil Nadu, India. Incidence and risk factors. Br J Psychiatry. 2002; Vol. 181:499–504.
18. Savarimuthu RJ, Ezhilarasu P, Charles H, Antonisamy B, Kurian S, Jacob KS. Post-partum depression in the community: a qualitative study from rural South India. Int J Soc Psychiatry. 2010; Vol. 56 (1):94-102.
19. Satija YK, Advani GB, Nathawat SS. Influence of stressful life events and coping strategies in depression. Indian J

Psychiatry. 1998; Vol. 40 (2):165-171.
20. Raju SS, Kumaraswamy N, Mani AJ. Socio-demographic factors of depressive disorders in India: A comparative appraisal. Indian J Psychiatry. 1980; Vol. 22 (4):356-360.
21. Patel V, Kirkwood BR, Pednekar S, Weiss H, Mabey D. Risk factors for common mental disorders in women Population-based longitudinal study. Br J Psychiatry. 2006; Vol. 189:547-555.
22. Singh GP, Chavan BS, Arun P, Lobraj, Sidana A. Geriatric Out-Patients with Psychiatric Illnesses in a Teaching hospital setting - A Retrospective Study. Indian J Psychiatry. 2004; Vol. 46 (2):140-143.
23. Depression: Epidemiology. Best Practice. BMJ. Available from: http://bestpractice.bmj.com/best-practice/monograph/55/basics/epidemiology.html. (Assessed on November 2011).
24. Reddy MS. Depression: The Disorder and the Burden. Indian J Psychol Med. 2010; Vol. 32 (1):1–2.
25. Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. Br J Psychiatry. 2004; Vol. 184:386-392.
26. Chivate AN, Patil SB, Wadkar KA, Naikwade NS, Chivate ND. A Systematic Review on Evaluation Methods of Antidepressants. Int J Drug Formul Res. 2011; Vol. 2 (2):27-42.
27. Mahal A, Karan A, Engelgau M. The Economic Implications of Non-Communicable Disease for India. Health, Nutrition and Population (HNP) Discussion Paper. Available from: http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1095698140167/EconomicImplicationsofNCDforIndia.pdf. (Assessed on December 2011).
28. Herrman H, Patrick DL, Diehr P, Martin ML, Fleck M, Simon GE, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO study. Functional status, health service use and treatment of people with depressive symptoms. Psychol Med. 2002; Vol. 32 (5):889-902.
29. Srivastava AS, Kumar R. Suicidal ideation and attempts in patients with major depression: Sociodemographic and clinical variables. *Indian J Psychiatry.* 2005; Vol. 47 (4):225-228.
30. Painuly N, Sharan P, Mattoo SK. Antecedents, concomitants and consequences of anger attacks in depression. *Psychiatry Res.* 2007; Vol. 153 (1):39-45.
31. MacHale S. Managing depression in physical illness. *Advances in Psychiatric Treatment*. 2002; Vol. 8:297-305.
32. Hays RD, Wells KB, Sherbourne CD, Rogers W, Spritzer K. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. *Arch Gen Psychiatry.* **1995; Vol. 52 (1):11-19.**
33. Gierz M, Jeste DV. Physical comorbidity in elderly Veterans Affairs patients with schizophrenia and depression. *Am J Geriatr Psychiatry.* 1993; Vol. 1 (2):165–170.
34. Proctor EK, Morrow-Howell NL, Dore P, Wentz J, Rubin EH, Thompson S, Li H. Comorbid Medical Conditions Among Depressed Elderly Patients Discharged Home After Acute Psychiatric Care. *Am J Geriatr Psychiatry*. 2003; Vol. 11 (3):329–338.
35. Satapathy R, Kar N, Das I, Kar GC, Pati T. A study of major physical disorders among the elderly depressives. *Indian J Psychiatry.* 1997; Vol. 39 (4):278-281.
36. Gupta A, Bahadur I, Gupta KR, Bhugra D. Self-awareness of depression and life events in three groups of patients: Psychotic depression, obsessive-compulsive disorder and chronic medical illness in North India. Indian J Psychiatry. 2006; Vol. 48 (4):251-253.
37. Brody BL, Gamst AC, Williams RA, Smith AR, Lau PW, Dolnak D, et al. Depression, visual acuity, comorbidity and disability associated with comorbid macular degeneration. Ophthalmology. 2001; Vol. 108 (10):1893–1900.
38. Banerjee A, Kumar S, Kulhara P, Gupta A. Prevalence of depression and its effect on disability in patients with age-related macular degeneration. Indian J Ophthalmol. 2008; Vol. 56 (6):469-474.
39. Gupta A, Deepika S, Taly AB, Srivastava A, Surender V, Thyloth M. Quality of life and psychological problems in patients undergoing neurological rehabilitation. Ann Indian Acad Neurol. 2008; Vol. 11 (4):225-230.
40. Jacob R, Kumar MS, Rajkumar R, Palaniappan V. A study to assess depression, its correlates and suicidal behaviour in epilepsy. Indian J Psychiatry. 2002; Vol. 44 (2):161-164.
41. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. Biol Psychiatry. 2003; Vol. 54 (3):388-398.
42. Ramachandran V, Parikh GJ, Srinivasan V. Depression in Hypertensive subjects. Indian J Psychiatry. 1983; Vol. 25 (4):260–263.
43. Grimsrud A, Stein DJ, Seedat S, Williams D, Myer L. The Association between Hypertension and Depression and Anxiety Disorders: Results from a Nationally-Representative Sample of South African Adults. PLoS One. 2009; Vol. 4 (5):e5552. doi:10.1371/journal.pone.0005552.
44. Shastri PC. Depression and cardiac disorders. Article available from: http://www.cnsindia.com/depression/medical_professional/educational/for_you/pdf/depression_and_cardiac_disorders.pdf. (Assessed on November 2011).
45. Raval A, Dhanaraj E, Bhansali A, Grover S, Tiwari P. Prevalence & determinants of depression in type 2 diabetes patients in a tertiary care centre. Indian J Med Res. 2010; Vol. 132:195-200.
46. Srinivasan K, Joseph W. A study of lifetime prevalence of anxiety and depressive disorders in patients presenting with chest pain to emergency medicine. Gen Hosp Psychiatry. 2004; Vol. 26 (6):470-474.
47. Demartini B, Masu A, Scarone S, Pontiroli AE, Gambini O. Prevalence of depression in patients affected by subclinical hypothyroidism. *Panminerva Med.* 2010; Vol. 52 (4):277-282.
48. van den Brink RHS, van Melle JP, Honig A, Schene AH, Crijns HJ, Lambert FP, et al . Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial infarction and Depression-Intervention Trial (MIND-IT). Am Heart J. 2002; Vol. 144 (2):219–225.
49. Leon FG, Ashton AK, D'Mello DA, Dantz B, Hefner J, Matson GA, et al. Depression and comorbid medical illness: Therapeutic and diagnostic challenges. J Fam Pract. 2003; Suppl: S19-S33.
50. Goodnick **PJ, Hernandez M: Treatment of depression in comorbid medical illness.** Expert Opin Pharmacother **2000**; 1(7):1367-1384.

51. Prieto **JM,** Atala **J, Blanch J, Carreras E,** Rovira M, Cirera E, et al. Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation. J Clin Oncol. 2005; Vol. 23 (25):6063-6071.
52. Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, et al. Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol.* 2002; Vol. 20 (7):1907-1917.
53. Tavoli A, Mohagheghi MA, Montazeri A, Roshan R, Tavoli Z, Omidvari S. Anxiety and depression in patients with gastrointestinal cancer: does knowledge of cancer diagnosis matter? BMC Gastroenterology. 2007; Vol. 7:28.
54. Pandey M, Sarita GP, Devi N, Thomas BC, Hussain BM, Krishnan R. Distress, anxiety, and depression in cancer patients undergoing chemotherapy. World J Surg Oncol. 2006; Vol. 4:68.
55. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clin Neurosci.* 2011; Vol. 13 (1):7–23.
56. Gitlin M, Altshuler LL, Frye MA, Suri R, Huynh EL, Fairbanks L, et al. Peripheral thyroid hormones and response to selective serotonin reuptake inhibitors. J Psychiatry Neurosci. 2004; Vol. 29 (5):383-386.
57. Foltyn W, Nowakowska-Zajdel E, Danikiewicz A, Brodziak A. Hypothalamic-pituitary-thyroid axis in depression. Psychiatr Pol. 2002; Vol. 36 (2):281-292.
58. Jackson IM. The thyroid axis and depression. *Thyroid.* 1998; Vol. 8 (10):951-956.
59. Demet MM, **Özmen** B, Deveci A, Boyvada S, Adıgüzel H, Aydemir O. Depression and Anxiety in Hyperthyroidism. Arch Med Res. 2002; Vol. 33 (6):552-556.
60. Awad AG. The Thyroid and the Mind and Emotions/Thyroid Dysfunction and Mental Disorders. Thyrobulletin. 2000; Vol. 7 (3).
61. Jadresic PD. Invited review: Psychiatric aspects of hyperthyroidism. J Psychosomatic Res. 1990; Vol. 34 (6):603-615.
62. Denicoff KD, Joffe RT, Lakshmanan MC, Robbins J, Rubinow DR. Neuropsychiatric manifestations of altered thyroid state. *Am J Psychiatry*. 1990; Vol. 147 (1):94–99.
63. Cooper DS. Hyperthyroidism. *The Lancet.* 2003; Vol. 362 (9382):459-468.
64. Howland RH. Thyroid dysfunction in refractory depression: implications for pathophysiology and treatment. J Clin Psychiatry. 1993; Vol. 54 (2):47-54.
65. Hickie I, Bennett B, Mitchell P, Wilhelm K, Orlay W. Clinical and subclinical hypothyroidism in patients with chronic and treatment-resistant depression. Aust N Z J *Psychiatry.* 1996; Vol. 30 (2):246-252.
66. Bahls SC, de Carvalho GA. The relation between thyroid function and depression: a review. Rev Bras Psiquiatr. 2004; Vol. 26 (1):40-48.
67. Fountoulakis KN, Iacovides A, Grammaticos P, St Kaprinis G, Bech P. Thyroid function in clinical subtypes of major depression: an exploratory study. *BMC Psychiatry.* 2004; Vol. 4:6.
68. Fountoulakis KN, Kantartzis S, Siamouli M , Panagiotidis P, Kaprinis S, Iacovides A, et al . Peripheral thyroid dysfunction in depression. The world journal of biological psychiatry the official journal of the World Federation of Societies of Biological Psychiatry. 2006; Vol. 7 (3): 131-137
69. Linnoila M, Lamberg BA, Potter WZ, Gold PW, Goodwin FK. High reverse T3 levels in manic and unipolar depressed women. *Psychiatry Res.* 1982; Vol. 6 (3):271-276.
70. Calloway SP, Dolan RJ, Fonagy P, De Souza VF, Wakeling A. Endocrine changes and clinical profiles in depression: II. The thyrotropin-releasing hormone test. Psychol Med. 1984; Vol. 14 (4):759-765.
71. Nemeroff CB. Clinical significance of psychoneuroendocrinology in psychiatry: focus on the thyroid and adrenal. J Clin Psychiatry. 1989; Vol. 50 (Suppl 13-20):13-20.
72. Loosen PT. The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker. Psychoneuroendocrinology. 1985; Vol. 10 (3):237–260.
73. Mason GA, Garbutt JC, Prange AJ. Thyrotropin-Releasing Hormone: Focus on Basic Neurobiology. In: Bloom FE, Kupfer DJ (Eds.) Psychopharmacology – 4th Generation of Progress. 2000. Availabe from: http://www.acnp.org/g4/GN401000048/CH048.html
74. Kraus RP, Phoenix E, Edmonds MW, Nicholson IR, Chandarana PC, Tokmakejian S. Exaggerated TSH responses to TRH in depressed patients with "normal" baseline TSH. J Clin Psychiatry. 1997; Vol. 58 (6):266-270.
75. Chakrabarti S. Thyroid Functions and Bipolar Affective Disorder. *J Thyroid Res.* 2011; doi:10.4061/2011/306367.
76. Kirkegaard C, Faber J. Free thyroxine and 3,3',5'-triiodothyronine levels in cerebrospinal fluid in patients with endogenous depression. Acta Endocrinol (Copenh). 1991; Vol. 124 (2):166-172.
77. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,30-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab. 2003; Vol. 88 (10):4551–4555.
78. Dugbartey AT. Neurocognitive aspects of hypothyroidism. Arch Intern Med. 1998; Vol. 158 (13):1413–1418.
79. Monzani F, Del Guerra P, Caraccio N, Pruneti CA, Pucci E, Luisi M, et al . Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Invest.* 1993; Vol. 71 (5):367–371.
80. Gulseren S, Gulseren L, Hekimsoy Z, Cetinay P, Ozen C, Tokatlioglu B. Depression, Anxiety, Health-Related Quality of Life, and Disability in Patients with Overt and Subclinical Thyroid Dysfunction. *Arch Med Res.* 2006; Vol. 37 (1):133-139.
81. Sabeen S, Chou C, Holroyd S. Abnormal thyroid stimulating hormone (TSH) in psychiatric long-term care patients. *Arch Gerontol Geriatr.* 2010; Vol. 51 (1):6-8.
82. Haggerty JJ Jr, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ Jr. Subclinical hypothyroidism: a modifiable risk factor for depression? Am J Psychiatry. 1993; Vol. 150 (3):508-510.
83. Fava M, Labbate LA, Abraham ME, Rosenbaum JF. Hypothyroidism and hyperthyroidism in major depression revisited. *J Clin Psychiatry.* 1995; Vol. 56 (5):186-192.
84. Kathol RG, Delahunt JW. The relationship of anxiety and depression to symptoms of hyperthyroidism using

operational criteria. Gen Hosp Psychiatry. 1986; Vol. 8 (1):23–28.
85. Trzepacz PT, McCue M, Klein I, Levey GS, Greenhouse J. A psychiatric and neuropsychological study of patients with untreated Grave's disease. Gen Hosp Psychiatry. 1988; Vol. 10 (1):49–55.
86. Kathol RG, Turner R, Delahunt J. Depression and anxiety associated with hyperthyroidism: Response to antithyroid therapy. *Psychosomatics.* 1986; Vol. 27 (7):501-505.
87. Suwalska A, Łącka K, Łojko D, Rybakowski JK. Quality of life, depressive symptoms and anxiety in hyperthyroid patients. *Rocz Akad Med Bialymst.* 2005; Vol. 50 (Suppl 1):61-63.
88. Bunevicius R, Velickiene D, Prange AJ. Mood and anxiety disorders in women with treated hyperthyroidism and ophthalmopathy caused by Graves' disease. *Gen Hosp Psychiatry.* 2005; Vol. 27 (2):133-139.
89. Röckel M, Teuber J, Schmidt R, Kaumeier S, Häfner H, Usadel KH. Correlation of "latent hyperthyroidism" with psychological and somatic changes. *Klin Wochenschr.* 1987; Vol. 65 (6):264-273.
90. Bommer M, Eversmann T, Pickardt R, Leonhardt A, Naber D. Psychopathological and neuropsychological symptoms in patients with subclinical and remitted hyperthyroidism. *Klin Wochenschr.* **1990; Vol. 68 (11):552-558.**
91. Schlote B, Schaaf L, Schmidt R, Pohl T, Vardarli I, Schiebeler H, et al. Mental and physical state in subclinical hyperthyroidism: investigations in a normal working population. *Biol Psychiatry.* 1992; Vol. 32 (1):48-56.
92. Schlote B, Nowotny B, Schaaf L, Kleinböhl D, Schmidt R, Teuber J, et al. Subclinical hyperthyroidism: physical and mental state of patients. *Eur Arch Psychiatry Clin Neurosci.* **1992; Vol. 241 (6):357-364.**
93. Lee IT, Sheu WH, Liau YJ, Lin SY, Lee WJ, Lin CC. Relationship of stressful life events, anxiety and depression to hyperthyroidism in an Asian population. Horm Res. 2003; Vol. 60 (5):247-251.
94. *Sonino* N, Fava GA, Belluardo P, Girelli ME, Boscaro M. Course of depression in Cushing's syndrome: response to treatment and comparison with Graves' disease. *Horm Res.* 1993; Vol. 39 (5-6):202-206.
95. *Rao* ML, Vartzopoulos D, Fels K. Thyroid function in anxious and depressed patients. *Pharmacopsychiatry.* 1989; Vol. 22 (2):66-70.
96. Tremont G. Neurobehavioral functioning in Thyroid disorders. Medicine and health. 2003; Vol. 86 (10): 318-22
97. Tappy L, Randin JP, Schwed P, Wertheimer J, Lemarchand-Béraud T. Prevalence of thyroid disorders in psychogeriatric inpatients: A possible relationship of hypothyroidism with neurotic depression but not with dementia. J Am Geriatr Soc. 1987; Vol 35 (6):526-531.
98. Gold MS, Pottash ALC, Extein I. Hypothyroidism and Depression. Evidence From Complete Thyroid Function Evaluation. *JAMA.* 1981; Vol. 245 (19):1919-1922.
99. Gupta S, Saha PK, Mukhopadhyay A. Prevalence of hypothyroidism and importance of cholesterol estimation in patients suffering from major depressive disorder. *J Indian Med Assoc.* 2008; Vol. 106 (4):240-242.
100. Joffe RT, Levitt AJ. Major depression and subclinical (grade 2) hypothyroidism. *Psychoneuroendocrinology*. 1992; Vol. 17 (2-3):215-221.
101. Oppedal RJ, Khan DA, Brown S. Hypothyroidism in Patients With Asthma and Major Depressive Disorder. Prim Care Companion *J Clin Psychiatry.* 2007; Vol. 9 (6):467–468.
102. Sintzel F, Mallaret M, Bougerol T. Potentializing of tricyclics and serotoninergics by thyroid hormones in resistant depressive disorders. *Encephale.* 2004; Vol. 30 (3):267-275.
103. Haggerty JJ Jr, Garbutt JC, Evans DL, Golden RN, Pedersen C, Simon JS, et al. Subclinical hypothyroidism: a review of neuropsychiatric aspects. *Int J Psychiatry Med*. 1990; Vol. 20 (2):193–208.
104. Oomen HA, Schipperijn AJ, Drexhage HA. The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. *Clin Endocrinol (Oxf).* 1996; Vol. 45 (2):215–223.
105. Konig F, Hippel C, Petersdorff T, Kaschka W. Thyroid autoantibodies in depressive disorders. Acta Med Austriaca. 1999; Vol. 26 (4):126–128.
106. Placidi GP, Boldrini M, Patronelli A, Fiore E, Chiovato L, Perugi G, et al . Prevalence of psychiatric disorders in thyroid disease patients. Neuropsychobiology. 1998; Vol. 38 (4):222–225.
107. White AJ, Barraclough B. Thyroid disease and mental illness: a study of thyroid disease in psychiatric admissions. *J Psychosom Res.* 1988; Vol. 32 (1):99–106.
108. Carta MG, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P. Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid autoimmunity. J Psychosom Res. 2002; Vol. 53 (3):789-793.
109. Counsell CE, Taha A, Ruddell WSJ. Coeliac disease and autoimmune thyroid disease. Gut. 1994; Vol. 35:844–846.
110. Velluzzi F, Caradonna A, Boy MF, Pinna MA, Cabula R, Lai MA, et al. Thyroid and celiac disease: clinical serological and echographic study. *Am J Gastroenterol*. 1998; Vol. 93 (6):976–979.
111. Nemeroff CB, Simon JS, Haggerty JJ Jr, Evans DL. Antithyroid antibodies in depressed patients. *Am J Psychiatry.* 1985; Vol. 142 (7):840-843.
112. Haggerty JJ, Evans DL, Golden RN, Pedersen CA, Simon JS, Nemeroff CB. The presence of antithyroid antibodies in patients with affective and non-affective psychiatric disorders. *Biol Psychiatry.* 1990; Vol. 27 (1):51-60.
113. Orenstein H, Peskind A, Raskind MA. Thyroid disorders in female psychiatric patients with panic disorder or agoraphobia. *Am J Psychiatry*. 1988; Vol. 145 (11):1428-1430.
114. Lesser IM, Rubin RT, Lydiard RB, Swinson R, Pecknold J. Past and current thyroid function in subjects with panic disorder. *J Clin Psychiatry.* 1987; Vol. 48 (12):473-476.
115. Brown RS. Chapter 15B – disorders of the thyroid gland in infancy, Childhood and adolescence. Available from: WWW.THYROIDMANAGER.ORG (accessed on December 2011).
116. Bongers-Schokking JJ and Keizer-Schrama SM. Influence of Timing and Dose of Thyroid Hormone Replacement on Mental, Psychomotor, and Behavioral Development in Children with Congenital Hypothyroidism. The Journal of Pediatrics. 2005; Vol. 147 (6): 768-774.
117. Simoneau-Roy J, Marti S, Deal C, Huot C, Robaey P, Van Vliet G. Cognition and behavior at school entry in children

with congenital hypothyroidism treated early with high-dose levothyroxine. J Pediatr. 2004; Vol. 144(6):747-52.
118. Pop AJM, de Rooy HAM, Vader HL, van der Heide D, van Son M, Komproe IH, et al. Postpartum Thyroid Dysfunction and Depression in an Unselected Population. *N Engl J Med.* 1991; Vol. 324 (25):1815-1816.
119. Lucas A, Pizarro E, Granada ML, Salinas I, Sanmartí A. Postpartum thyroid dysfunction and postpartum depression: are they two linked disorders? Clin Endocrinol (Oxf). 2001; Vol. 55 (6):809-814.
120. Bunevicius R. Depressive disorder and thyroid axis functioning during pregnancy. *World J Biol Psychiatry*. 2009; Vol. 10 (4):324-329.
121. Harris B, Othman S, Davies JA, Weppner GJ, Richards CJ, Newcombe RG, et al. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. *BMJ.* 1992; Vol. 305 (6846):152-156.
122. Burman KD, Ross DS, Mulder JE. Postpartum thyroiditis. UpToDate. Available from: http://www.uptodate.com/contents/postpartum-thyroiditis?source=search_result&search=thyroid+dysfunction+and+depression&selectedTitle=11~150. (Assessed on November 2011).
123. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007; Vol. 92 (8 Suppl):S1-S47.
124. Kuijpens JL, Vader HL, Drexhage HA, Wiersinga WM, van Son MJ, Pop VJ. Thyroid peroxidase antibodies during gestation are a marker for subsequent depression postpartum. *Eur J Endocrinol.* 2001; Vol. 145 (5):579-584.
125. McCoy SJB, Beal JM, Payton ME, Stewart AL, DeMers AM, Watson GH. Postpartum Thyroid Measures and Depressive Symptomology: A Pilot Study. J Am Osteopath Assoc. 2008; Vol. 108 (9):503-507.
126. Neale DM, Cootauco AC, Burrow G. Thyroid Disease in Pregnancy. Clin Perinatol. 2007; Vol. 34 (4):543-557.
127. Postpartum Thyroiditis. American Thyroid Association. Article available from: http://www.thyroid.org/patients/brochures/Postpartum_Thyroiditis_brochure.pdf. (Assessed on November 2011).
128. Berndt ER, Finkelstein SN, Greenberg PE, Howland RH, Keith A, Rush AJ, et al. Workplace performance effects from chronic depression and its treatment. *J Health Econ.* 1998; Vol. 17 (5):511-535.
129. Simon GE. Social and economic burden of mood disorders. Biol Psychiatry. 2003; Vol. 54 (3):208-215.
130. Coulehan JL, Schulberg HC, Block MR, Madonia MJ, Rodriguez E. Treating depressed primary care patients improves their physical, mental, and social functioning. Arch Intern Med. 1997 May 26;157(10):1113-20.
131. Cooper R, Lerer B. The use of thyroid hormones in the treatment of depression. *Harefuah.* 2010; Vol. 149 (8):529-534.
132. Joffe RT. Psychopharmacology for the Clinician. Revue de psychiatrie & de neuroscience. 2002; Vol. 27 (1): 80.
133. Baumgartner A. Thyroxine and the treatment of affective disorders: an overview of the results of basic and clinical research. The International Journal of Neuropsychopharmacology. 2000; Vol. 3:149-165.
134. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,30-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab.* 2003; Vol. 88 (10):4551–4555.
135. Rack SK, Makela EH. Hypothyroidism and depression: a therapeutic challenge. Ann Pharmacother. 2000; Vol. 34 (10):1142-1145.
136. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange Jr AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med.* 1999; Vol. 340 (6):424–429.
137. Altshuler LL, Bauer M, Gitlin MJ, Mintz J, Szuba MP, Leight KL, et al . Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry*. 2001; Vol. 158 (10):1617–1622.
138. Stagnaro-Green A. Postpartum thyroiditis. Best Pract Res Clin Endocrinol Metab. 2004; Vol. 18 (2):303–316.
139. Stagnaro-Green A. Postpartum Thyroiditis: The Case For Selective Screening. J Clin Endocrinol Metab. 1999; Vol. 84 (6):1819-1821.
140. Harris B, Oretti R, Lazarus J, Parkes A, John R, Richards C, et al. Randomised trial of thyroxine to prevent postnatal depression in thyroid-antibody-positive women. *Br J Psychiatry.* 2002; Vol. 180:327–330.
141. Heinrich, TW, Grahm G. Hypothyroidism presenting as psychosis: Myxedema madness revisited. Prim Care Companion J Clin Psychiatry. 2003; Vol. 5 (6):260–266.
142. Corruble E, Berlin I, Lemoine A, Hardy P. Should Major Depression with 'High Normal' Thyroid-Stimulating Hormone Be Treated Preferentially with Tricyclics? Neuropsychobiology. 2004; Vol. 50 (2):1-3.
143. Baskin J et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism. AACE Thyroid Task Force. *Endocrine Practice.* 2002; Vol 8 (6):457-469.
144. Almeida OP, Alfonso H, Flicker L, Hankey G, Chubb SA, Yeap BB. Thyroid hormones and depression: the health in men study. *Am J Geriatr Psychiatry.* 2011; Vol. 19 (9):763-770.
145. Kim JM, Stewart R, Kim SY, Bae KY, Yang SJ, Kim SW, et al. Thyroid stimulating hormone, cognitive impairment and depression in an older korean population. *Psychiatry Investig.* 2010; Vol. 7 (4):264-269.
146. Roberts LM, Pattison H, Roalfe A, Franklyn J, Wilson S, Hobbs FD, et al . Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? *Ann Intern Med.* 2006; Vol. 145 (8):573-581.
147. Andrade Junior NE, Pires ML, Thuler LC. Depression and anxiety symptoms in hypothyroid women. *Rev Bras Ginecol Obstet.* 2010; Vol. 32 (7):321-326.
148. Basraon S, Costantine MM. Mood Disorders in Pregnant Women With Thyroid Dysfunction. Clinical Obstetrics & Gynaecology. 2011; Vol. 54 (3): 506–514.
149. Stagnaro-Green A. Postpartum Thyroiditis. J Clin Endocrinol Metab. 2002; Vol. 87 (9):4042-4047.

Notes

Notes