REVIEW ARTICLE

Challenges in Management of Major Depression in Patients with co-Morbid Medical Conditions

Vikas Menon[1] Pooja Patnaik Kuppili[2]

1-Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER); 2- All India Institute of Medical Sciences

ABSTRACT

Depression is a heterogeneous illness and depression with co-morbid physical illness may represent a phenotype of depression. Concurrent medical illness in depression is associated with greater functional and social impairment and significantly higher health care costs. A variety of mechanisms including lifestyle factors, immune-inflammatory pathways, medications and psychological factors have been proposed to explain the association between depression and physical illness. However, each of these pathways engenders unique challenges in managing such patients. Of utmost importance is to establish the nature of the underlying medical or psychological cause(s) which will inform customized management plans. This article initially reviews the prevalence of depression in medical conditions and vice versa. Subsequently, we move on to discuss specific approaches to diagnosis of depression in the context of medical co-morbidity. Finally, we describe evidence based pharmacological and psychosocial intervention strategies with some recommendations for common clinical scenarios. Evidence based care models to manage depression with physical illness are described which may be adapted for use in low resource settings.

Keywords: Depression, depressive disorder, co-morbidity, psychosomatic medicine; consultation-liaison psychiatry; psychiatry

INTRODUCTION

Problem statement

Depression is one of the top contributors of disability globally in terms of Disability Adjusted Life Years superseding physical illnesses like Diabetes Mellitus, Hypertension.[1] In a multination study conducted by World Health Organization (WHO), nearly 69% of patients suffering from depression presented with physical complaints in the primary care setting.[2]

Healthcare costs incurred in patients with depression with physical illness were found to be significantly higher compared to those without depression.[3,4] Further, the co-morbidity of depression with medical illness has been associated with significantly greater impairment in functioning, poor quality of life, poor adherence to treatment, worsening of physical illness as well as higher mortality.[5] Hence, depression and physical illness occurring together is not only a challenging clinical problem but also assumes a greater public health relevance. In this paper, we aim to give an overview of the prevalence of depression in medical illness and vice versa and discuss commonly implicated mechanisms for this observed association. We then, summarize the four approaches used to commonly assess and diagnose depression in the medically ill. Finally, we discuss evidence based management of depression with medical co-morbidities both from a pharmacologic and psychosocial perspective.

Address for Correspondence: Dr V Menon
Department of Psychiatry
JIPMER, Puducherry-605006
Email: drvmenon@gmail.com

Prevalence of depression in physical disorders

Depression is often found as a co-morbidity in physical illnesses afflicting various organ systems of the body. Among the physical illnesses, relatively higher rates of depression have been noted in patients with neurological illness. The prevalence of depression in Parkinson Disease (PD) and epilepsy was found to range from 2.7% - 90%, 20%-55% and 14%-19% respectively.[5] Prevalence of depression in Diabetes mellitus (DM) was found to range from 3.8% - 49.5%.[6] Interestingly, the prevalence of depression in diabetes was found to be higher in the lower and middle income countries as compared to the high income countries.[7]

Neoplasms and cardiovascular diseases have also shown a significant depressive burden. Co-morbid depression was found among 8% - 50% of sufferers with cancer[8] while nearly a third of survivors with Myocardial Infarction (MI) had clinically significant depression.[9]. The latter is particularly relevant as depression has been found to be associated with a robust threefold increased risk of cardiac mortality among MI survivors.[10]

The varying prevalence could be due to several factors such as missing the diagnosis of depression due to overlap of symptoms between physical illness and depression, differences in tools of assessment or diagnostic criteria used, poor mental health literacy among patients as well as the physicians, stigma etc.

Prevalence of medical co-morbidity in depression

Akin to the occurrence of depression as co-morbidity in almost all organ systems of the body, patients with depression have been consistently found to be at higher risk of developing medical illnesses. A cross sectional large Korean study assessed age adjusted prevalence ratios (APR) of various chronic physical illness in patients with depression. The authors found that the chronic physical illness with the highest APR was asthma amongst adult males and females and chronic renal failure in the elderly age group.[11] A meta analysis of prospective studies reported that depression is associated with 60% higher risk of Diabetes Mellitus.[12]

Patients with depression were found to be at a greater risk of developing Alzheimer's disease compared to those without depression.[13] Prospective meta-analyses have shown that depression is prospectively associated with increased risk of developing myocardial infarction as well as stroke.[14,15] Depression is also linked to a small but significant increased risk of developing breast cancer.[16]

Proposed mechanisms linking depression and medical illness

Immuno-inflammatory pathways are gaining credence in explaining the close links between depression and physical illness. Proinflammatory state characterised by increase of interleukin-1α and β (IL-1α and IL-1β), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) is seen in patients with several chronic physical illnesses as well as depression.[17,18] The increase of cytokines precipitates alterations in the hypothalamo-pituitary-adrenocortical axis, serotonergic and noradrenergic activity which is intricately tied to depression. Further, the administration of cytokines has been demonstrated to induce sickness behaviour in animal models which closely mimics the depression phenotype in humans.[19]

Medications used to treat several physical illnesses such as beta blockers, calcium channel blockers, interferon, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, anti-obesity drugs, steroids have been reported to cause depression.[20] Lifestyle factors and unhealthy choices stemming from depression such as poor diet, physical inactivity and substance use can also mediate occurrence of co-morbidity of depression and physical illness.[21] In psychological terms, a chronic physical illness can be viewed as a threat to one's existence of life which could trigger depression.[22]

Assessment of depression in the medically ill

The detection of depression in the medically ill poses unique challenges and pitfalls. Many clinicians tend to view depression as a legitimate and understandable reaction to the diagnosis and experience of a physical illness that does not require treatment. Some patients with medical illness experience a sense of futility and powerlessness; the characteristics of a demoralization experience.[23] However, negative non-pathological reactions to physical illness tend to be sub-syndromal and self-limiting. This is in contrast to a true syndromal depression which tends to take a course of its own and is not merely tied to the given stressor.[24] Adjustment disorder is a closely related maladaptive emotional state that may also be associated with significant functional impairment but often does not require pharmacologic treatment.[25] Sometimes, pathological mood states may be in response to inadequately managed physical symptoms. Asking simple questions like whether, physical factors are the reason for their 'blues' or removing them may make improve their mood can unmask the physical symptoms that require attention.[26]

The spectrum of emotional reactions in medical illness, therefore, can range from distressed states characterized by demoralization and hopelessness, to maladaptive state of negative adjustment and finally, a pathological 'true' depression. In order to differentiate depression from non-pathological mood states, a clinician must consider the nature, intensity, duration and burden of symptoms. In a state of demoralization, a sense of powerlessness and futility dominate the picture whereas anhedonia and lassitude characterize the experience of depression.[23]. The distinction between normal and pathological is, often, a matter of clinical judgment aided by key informant's descriptions about the habitual reactions of patient to stress as well as the cultural contextualization of the behaviour.

Several medical disorders can themselves, induce depressive symptoms, either through common pathophysiological pathways such as neuroinflammation, as a consequence of bodily perturbations induced by the physical illness as well as psychological pathways.[27,28] Furthermore, many established pharmacological agents, approved for treating medical conditions, can induce depression. For instance, treatment with antihypertensives such as calcium channel blockers and interferon alpha has been shown to induce depression.[29] A careful review of records will suggest a temporal link between initiation of medications and onset of depressive symptoms. The timeline approach can also be used to distinguish primary depression, arising from biological diathesis or from psychosocial factors, from a secondary depression due to the physiological effects of a medical illness. In the former, depression is already present and the medical condition is added on while in the latter, medical illness precedes depression.

Depression may, often, be camouflaged by medical complaints and go unnoticed in the absence of a careful assessment. A case in point is the depressive pseudodementias.[30] Here, it is the cognitive complaints that are most prominent and only a thorough enquiry may unmask the underlying mood symptoms and fatiguability that points to an underlying depression. Cultural preferences for expressing distress through somatic, rather than psychological symptoms may also cause confusion whether the depression is secondary to physical symptoms, particularly to a physician unfamiliar with cultural nuances.[31] Pain symptoms, either standalone or disproportionate to physical findings, are

another example of how depression may be masked through somatically focussed presentation. Depression, through its physiologic effects on nociceptive pathways can heighten the experience of pain. The clinician needs to be wary of pursuing a typically unrewarding journey of aggressively investigating the cause of pain and instead, consider the possibility of an underlying depression.[32]

Less commonly, depression may be falsely apparent and mask an underlying physical or mental illness. Hypoactive delirium, seen in the medically ill, is often mistaken for depression as patients are typically inert, withdrawn, sleepless and inattentive.[33] However, the acute onset and fluctuating clinical picture are key differentiators from a depression. Some varieties of dementia may present initially as a depression with shared features such as amotivation and affective restriction. Alcohol or prescription drug intoxication can sometimes, cause a behavioural syndrome resembling the depressive phenotype and may require sufficient a period of observation following sobriety to confirm an underlying depression.[34,35]

In order to circumvent these potential pitfalls and enhance the validity of diagnosis of depression in the medically ill, researchers have suggested the following approaches:[36]

1. Inclusive Approach – This approach does not discriminate between symptoms on the basis of their cause. Essentially, it utilizes all symptoms of depression to arrive at a diagnosis regardless of whether it is primary or secondary to the physical condition. While this approach may offer a high sensitivity of diagnosis, the specificity is low.

2. Exclusive Approach – This approach advocates the exclusion of two common symptoms of the depression phenotype, namely fatigue and appetite/weight changes. In other words, these two symptoms are not counted towards making a diagnosis of depression as they can commonly be a consequence of physical illness. This approach may yield more specificity but its sensitivity is low.

3. Etiologic Approach – This approach seeks to exclude symptoms which are deemed to be a direct consequence of the physical illness when making the diagnosis of depression. This approach is used by the Structured Clinical Interview for DSM. The practical problem with this theoretically robust and accurate approach is that the determination of symptoms being the result of a physical illness is left to the judgment of the clinician. Thus, in the absence of a standardized assessment scheme, it will have low inter rater reliability. It is another matter that psychiatrists, leave alone non-psychiatrist physicians, may never become knowledgeable about the entire gamut of medical conditions to reliably infer whether depression is a physiological fallout of the medical disease.

4. Substitutive Approach – This approach seeks to resolve the impasse over the cause of symptoms and advocates substituting somatic symptoms, such as fatigue, for psychological or cognitive symptoms such as hopelessness or pessimism. More specific examples of substituting symptoms have been suggested by Endicott. On the flip side, there is poor consensus on what symptoms can or should be substituted and whether it depends on the physical illness in question. Descriptors and rubrics covering selection of criteria, application and rationale for using alternate symptoms have been suggested by Endicott to enhance the validity of this approach.

Given the inadequacies of each of these approaches, a more eclectic approach to diagnosis of depression incorporating elements from all four, may yield more accuracy in diagnosis of depression. This has to be balanced against the risk of being overly restrictive in making a diagnosis as well as the time constraints of a busy clinician, which precludes detailed and comprehensive assessment required in an eclectic approach.

Management of depression in the medically ill Somatic treatments and considerations therein

Treating depression in the setting of medical co-morbidities involves subtle challenges and concerns. Many of the standard anti-depressants used for conventional depression have also been found to be efficacious for treating depression in the presence of medical co-morbidities. The two major physician and patient concerns here involve drug interactions and adverse drug reactions to pharmacologic treatment.

Many of the Selective Serotonin Reuptake Inhibitors are also potent CYP2D6 inhibitors. This may lead to clinically significant drug interactions with many anti-epileptics, antibiotics as well as anti-retroviral agents. Side effects to these agents may appear at relatively lower dosages when co-initiated on SSRI's. Many patients may also be slow or intermediate metabolizers of these agents by the P450 enzymes, thus resulting in accumulation of the unmetabolized drug and further side effects. Among the SSRI's, sertraline and escitalopram have relatively fewer drug interactions and hence may be chosen in those with complex concurrent medication regimens.[37]

It is a sound practice to choose medications in order to leverage their side effect profile to the patient's advantage. A case in point is the usage of mirtazapine or trazodone for the medically ill who are depressed and also experiencing prominent insomnia. Similarly, for patients who experience co-morbid neuropathic pain with depression, evidence suggests that dual acting anti-depressants such as Tricyclic Anti-depressants or Duloxetine may prove to be beneficial in tackling both symptoms.[38] Stimulants such as methylphenidate and bupropion have been used with some success in de-

pression with concurrent fatigue as well as in generally debilitated patients in whom motivation and energy levels may improve with the use of stimulants.[39]

Somatic treatments such as electroconvulsive therapy have been employed successfully in managing depression presenting with a range of co-morbid medical conditions. Often, due to general debility or obtundation, patients are unable to consume or tolerate oral anti-depressants. In such situations, ECT offers a rapidly acting alternative to oral medications. ECT is preferred for depressions presenting with high degree of suicidality, stupor, inanition, intolerance to oral medications or treatment resistant varieties of depression, all of which are commonly encountered in the setting of medical co-morbidity.[40,41] Other related therapies such as repetitive Transcranial Magnetic Stimulation (rTMS) has been used to treat depression with a range of co-morbid neurological conditions such as parkinsonism, stroke and epilepsy.[42] Available open studies using vagal nerve stimulation and deep brain stimulation have shown mixed results thus far and better quality evidence is awaited.[43]

A major concern when using anti-depressants in the medically ill is the increased propensity for side effects. Often, the volume of distribution available for the drug is reduced due to the altered fluid balance and weight profiles of the depressed medically ill subjects. Moreover, hepatic and renal functions are often below par and contribute to the body's inability to metabolize and eliminate drugs in a timely manner. All this may lead to adverse effects even from routine dosing regimens used for non-medical populations. It is therefore, a good practice to start lower dosages and go slower with the titration protocols for various anti-depressants. For drugs with a narrow therapeutic index such as lithium, the safety margin is reduced further and more aggressive serum monitoring may be needed to preempt drug toxicity apart from starting lower dosages of such agents. Other medications, with a better safety profile, may need to be considered in the medically ill.

An important cause of sudden death syndrome in the medically ill following the use of psychiatric drugs is the induction of cardiac conduction disturbances, prominently QTc prolongation.[44] It is therefore imperative that the cardiac safety profile of drugs is analysed before choosing the anti-depressant. This information can be easily obtained from the existing pharmacopoeia. Generally, these patients are at high risk for delirium and sensitive to anti-cholinergic medications which can potentially, precipitate delirium in this population.[45] Hence, it is a good practice to reconsider the use of agents such as TCA's or paroxetine, known for its prominent anti-cholinergic property among SSRIs, as first line agents to treat depression in this group. Often, these patients have very complex medication regimens and the total anti-cholinergic load may need to be carefully monitored. One must also keep in mind that excessive use of sedative-hypnotics can also precipitate delirium in this group and therefore, these agents need to be used judiciously.[46]

Serotonin syndrome is another potential complication that must be kept in mind, particularly, when patients are put on several serotonergic agents concurrently or when co-initiated on SSRIs and certain anti-biotics such as linezolid, a reversible Monoamine Oxidase Inhibitor-I (MAO-I).[47] In such cases, it may be prudent to initiate SSRIs with a shorter half-life (for instance, sertraline) or employ non-serotonergic anti-depressants such as bupropion, though a reasonable index of suspicion for serotonin syndrome is still advised when using these agents concurrently owing to isolated reports.

Preliminary evidence suggests that intravenous ketamine may be a rapidly acting anti-depressant in the terminally ill, often brightening the mood within hours of the first dose.[48,49] This suggests that agents targeting the N-Methyl D-Aspartate Receptor may hold some promise and merits further investigation for sustained efficacy and safety profiles.

Evidence for psychotherapeutic interventions

Several challenges are involved in effectively utilizing psychotherapeutic interventions for the depressed medically ill. Such patients can be difficult to engage properly, owing to on-going medical issues. Their ego strength, already subjected to considerable demands due to the medical illness, may not have sufficient reserves to deal with issues arising out of dynamic and exploratory therapies. Many of the reported somatic symptoms may overlap with those due to physical causes. Consequently, determining treatment response may be tricky and require greater consideration of non-overlapping symptoms.

Typically, patient's coping strategies are often overwhelmed by the stress of medical illness and the changed personal and societal role that are common fallouts.[5] Quite often, the psychiatrist may assist patients in adapting their coping strategies to deal with these novel situations. Referral to support groups or helping patients to stay connected with their families and existing sources of support while in the hospital can maintain their morale and boost coping skills. Basic tweaking of the ward schedules such as avoidance of night time tests, incorporating exercise training as part of activity scheduling and maintaining a relaxing nocturnal environment can promote a good night's sleep and resultantly, coping.[50,51]

As mentioned earlier, medical illness frequently involves changes in personal, familial and societal roles for the depressed patient. Interpersonal therapy, with its focus on role disputes and role transitions have been found to be efficacious in the depressed medically ill.[52] Cognitive Behavior Therapy (CBT) has also been found to be useful and targets automatic thoughts, dysfunctional cognitive assumptions and behavioural activation aimed at ending the cycle of physical inactivity and depression in medically ill.[53–55]

More than a decade ago, Griffith and Gaby[23] described a basis for using existential or narrative therapies, ultimately aimed at improving coping, among the depressed medically ill. They theorized the presence of

"existential postures" which are basically passive dysfunctional attitudes that patients may take in the context of severe medical illness, when usual adaptive coping strategies are overwhelmed. Examples of such postures may include despair, meaninglessness, helplessness, despair and isolation. They went on to describe a brief existential psychotherapy model where the patient and therapist jointly explores distressing illness related themes and its negative effects on their life's pursuits negatively, all the while seeking to normalize patient distress. The next step involves the patient and physician jointly tailoring an active strategy for tackling the situation. As therapy progresses, negative attitudes are converted into positive feelings such as hope, coherence, a sense of purpose and so on. Emerging evidence supports the efficacy of an integrated CBT and existential therapy intervention among the severely ill and depressed.[56]

Several integrated psychosocial treatment models, targeting a variety of barriers to treatment of depression in the medically ill individuals have been developed. Two specific models that appear promising are the Personalized Adherence Intervention for Depression and COPD (PID-C) and the Ecosystem Focussed Therapy; developed initially for post stroke depression.[57] These therapies target reduction of barriers to patient engagement, enhancing adherence to treatment recommendations and weathering the "psychosocial storm" resulting from patient's disability and its fallout on family routines. Preliminary evidence for both these models have been encouraging.[58,59]

Social interventions, based on support groups,[60] can be useful to provide an atmosphere of trust and respect wherein the patient can raise key concerns, fears and draw upon suggestions from others who may have gone through similar experiences. There are many dedicated foundations and organizations dedicated to specific illness and they offer options to connect, uplift and support patients and their families. The latter group is often overlooked but it is true that meaningful support may also be required for the family members involved in caring for the depressed medically ill, an act which can take a significant mental and emotional toll on all those involved.[61]

Particular attention and timely supportive intervention needs to be given to physicians and nurses who may feel burnt out during this challenging process of caregiving for the severely ill. Many a clinician has complained of the feelings of isolation and helplessness that accompanies this process.[62] Bringing in team leaders who are familiar with the nuances of rotating health care personnel and who are themselves role models of good self-care can mitigate or even prevent these reactions.

Lately, a health care delivery trend that is gaining significant traction in the management of the medically ill, is the 'medical home' approach.[50,63] This essentially involves multidisciplinary management in the setting that suits the patient's primary illness. This facilitates co-ordinated and prompt services apart from the convenience of getting all services in a single location from a patient perspective. Variations of this model include the vertical integration of services where the specialist psychiatrist may offer their services by visiting the primary health centre, either at pre-defined schedules or on a daily basis.[64–66] Telepsychiatry approaches, wherein the psychiatrist can offer his/her expert opinion on managing depression while being geographically dispersed from the medical team, offers a viable cost-effective strategy that may have relevance in low resource settings like ours where there is an acute shortage of trained mental health professionals. Another cost-effective strategy which may have relevance for low resource settings is the integrated collaborative care approach.[67] This approach emphasizes a vertical integration of primary care with specialist mental health care and includes both treatment components such as lifestyle modifications as well as measures to improve referrals and linkage systems which would enhance service delivery.

CONCLUSION

Management of depression with concurrent medical illness poses several unique challenges. Good diagnostic skills and structured evaluation approaches are required to delineate depression from the mirage of overlapping, non-specific symptoms. Specific considerations while initiating pharmacotherapy include the safety and drug interaction profiles of chosen agents. A wealth of evidence based psychosocial intervention strategies is available to address the needs of the patient, family and caring team, who form a veritable therapeutic triangle in day to day practice. Future research must focus on developing high quality evidence for collaborative health care models as well as optimizing the uptake and sustainability of psychosocial interventions for the depressed medically ill.

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