State of the art in the care of the depressed patient

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ABSTRACT

Background: Depression continues to be a major cause of morbidity and mortality. Depression is a common debilitating illness that can happen to anyone, at any age, and to people of any race or ethnic group. Females are more vulnerable than males; one out of four women may have depression sometime during their lifetime. Despite the wide range of people who suffer from this serious disorder and the associated high risk of death from suicide, only 20 percent are currently receiving treatment. Moreover, it is well recognized that depression greatly contributes to fatality associated with heart disease. The 1990 Global Burden of Disease Study ranked depression as the fourth leading disease burden worldwide as measured by life-years lost to disability, and it is projected to be ranked as the second leading disease burden by the year 2020. In light of these statistics, there is a clear need to address the impact of this condition and to develop new methods to adequately diagnose and treat those who suffer.

Objective: The objective of this paper is to highlight recent developments regarding treatment and care of the depressed patient.

Method: A review of recent literature on the neurobiology of depressive disorder, and its reflection on the care and treatment of the depressed patient formed the matrix for this paper.

Neurobiology of depression: Evidence from neuroscience, genetics, and clinical investigation demonstrate that depression is a disorder of the brain. Modern brain imaging technologies are revealing that in depression, neural circuits responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly, and that critical neurotransmitters are perhaps out of balance. Genetics research indicates that vulnerability to depression results from the influence of multiple genes acting together with environmental factors. Studies of brain chemistry and of mechanisms of action of antidepressant medications continue to inform the development of new and better medical and psychotherapy treatments. STAR*D, a large study funded by the National Institutes for Mental Health, found that less than half of patients got completely well after a single antidepressant was taken, and although more patients got well once they were switched to another medicine, the proportion of those who got better decreased each time a person had to switch to another medication.

Treatment of depression: Recent advances in treatment have occurred for patients with mood disorders, these include: pharmacotherapy, combined psychotherapy pharmacotherapy, and novel physical therapies. The focus of new drug development reflects a shift from serotonin specificity to combine or specific noradrenergic activity. The efficacy of sequencing cognitive therapy after anti-depressant treatment in patients who were partially remitted was examined recently by Paykel and colleagues. The cumulative relapse rate was reduced significantly from 47% in the clinical management control group to 29% in the group that received 16 sessions of cognitive therapy.

Conclusion: Improved recognition, treatment, and prevention of depression are critical public health priorities. The administration of combination of treatment interventions and dual reuptake inhibitors are likely to ensure early response and prevention of relapse. Recovery of function ought to be the target of any treatment plan.

الجديد في العناية بالمريض المصاب بالكآبة

الخلاصة

خلفية البحث: لاتزال الكآبة سبباً في حصول المراضة والوفاة فهي تؤدي إلى الوهن والضعف، قد تصيب أي شخص وفي أي عمر بغض النظر عن العرق أو العنصر. والإناث أكثر من الذكور عرضة للإصابة، فهي تصيب واحدة من كل أربعة إناث خلال الحياة. وبالرغم من أن شريحة واسعة من الناس يعانون منها ومما يرافقها من خطورة الإقدام على الإنتحار، إلا أن الذين يحصلون على العلاج لا يتعدون الـ ٢٠%، ولا يقتصر موت المصاب على تعرضه للإنتحار فقط، بل إن الكآبة تعرض المصاب إلى الوفاة من النوبات القلبية ايضا. وجدير بالذكر أن إحدى الدراسات العالمية التي أجريت في عام ١٩٩٠ لقياس عبئ الأمراض الشامل على المجتمعات وجدت الكآبة من بين أهم أربع أمراض التي يحصل منها العبؤ المرضي الشامل، وتتنبأ نفس الدراسة أن تصبح الكآبة المرض الثاني المسبب لهذا العبئ وذلك في عام ٢٠٢٠ . وفي ضوء ما تقدم تبرز الحاجة إلى إعطاء إهتمام أكبر لمواجهة عواقب الإصابة بالكآبة وإلى المزيد من البحث والتقصي للوصول إلى أساليب فعالة لتشخيصها وعلاجها مبكراً.

هدف البحث: تهدف هذه الدراسة إلى إلقاء الضوء على أحدث المستجدات في مجال العلاج والعناية بالمصاب بدآء الكآبة.

طريقة البحث: مراجعة أحدث الأدبيات التي تتصدى للبيولوجية العصبية لداء الكآبة وانعكاسات ذلك على علاج المصاب والعناية به.

البيولوجية العصبية للكآبة: المؤشرات البحثية في العلوم العصبية والجينية والتحريات السريرية تدل على أن الكآبة اضطراب دماغي المنشأ، وظهر من خلال تقنيات تصوير الدماغ أن الدوائر العصبية في الدماغ والمسؤولة عن تنظيم المزاج والتفكير والنوم والشهية للأكل والسلوك بصورة عامة لا تعمل بصورة سليمة، وأن الناقلات العصبية غير متوازنة. وتدل البحوث الجينية على أن الكآبة تحصل بفعل جينات متعددة وللتفاعل بين تلكم الجينات مع بعض العوامل البيئية. وتؤسس بحوث كيميائية الدماغ وآلية عمل مضادات الكآبة إلى إكتشاف عقاقير علاجية وعلاجات نفسية أفضل. وأن دراسة STAR"D المشهورة الممولة من المعاهد القومية للصحة النفسية أظهرت أن أقل من نصف المصابين بالكآبة يستجيبون إلى العلاج بمضاد إكتئاب واحد بالرغم من أن العديد من المصابين يظهرون تحسناً عندما يتحولون الى مضاد للإكتئاب مختلف ولكن نسبة هؤلاء أخذ بالتناقص.

علاج الإكتئاب: تتركزالمستجدات الحديثة في علاج الكآبة على العلاج الدوائي والعلاج الدوائي المدعوم بالعلاجات النفسية وعلاجات طبيعية مبتكرة. وتميل العلاجات الدوائية الحديثة الى التحول من أدوية تؤثرفي السيروتونين الى عقاقير تؤثر في السيروتونين والنورأدرينالين مجتمعا. هذا وقد بحث Paykel وزملائه في دور العلاج المعرفي المضاف إلى علاج المصابين الذين سبق وأبدوا تجاوبا جزئيا للعلاج بالعقاقير المضادة للكآبة فوجدوا أن النسبة التراكمية للإنتكاسات لديهم إنخفضت من ٤٧% إلى ٢٩% بعد ستة عشر جلسة علاج معرفي.

الإستنتاج: إن العمل على تطويرأساليب تشخيص الكآبة وعلاجها والوقاية منها يشكل إحدى الأولويات المهمة لخدمات الصحة العامة، وإن من شأن الجمع بين مداخلات علاجية متعددة أو إستخدام عقاقير ذات فاعلية مزدوجة في التأثيرعلى ناقلات عصبية متعددة ، من شأن ذلك أن يقلل من نسب الإنتكاسة والوقاية من الكآبة، ولابد أن يكون الهدف النهائي للعلاج هو عودة المصاب إلى الحالة الوظيفية السليمة التي كان يتمتع بها قبل الأصابة وعدم الإكتفاء بالإستجابة الجزئية او التهاود النسبي للأعراض.

Depression is a brain disease associated with widespread impairment in biopsychosocial functioning, and continues to be a major cause of morbidity and mortality. Depression is a common debilitating illness that can happen to anyone, at any age, and to people of any race or ethnic group. Females are more vulnerable than males; one out four women may have depression sometime during their lifetime. Despite the wide range of people who suffer from this serious disorder and the associated high risk of death from suicide, only 20 percent are currently receiving treatment. Moreover, it is well recognized that depression greatly contributes to fatality associated with heart disease. The 1990 Global Burden of Disease Study ranked depression as the fourth leading disease burden worldwide as measured by life-years lost to disability, and it is projected to be ranked as the second leading disease burden by the year 2020 after ischemic heart disease, and the first leading disease burden by the year 2030. In light of these data, there is a clear need to develop new methods to adequately diagnose and

treat those who are overwhelmed by depressive disorders.

Evidence from neuroscience indicated that depression is a disorder of the brain. Modern brain imaging technologies are revealing that, in depression, neural circuits responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly, and that critical neurotransmitters are perhaps out of balance. Genetics research indicates that vulnerability to depression results from the influence of multiple genes acting together with environmental factors. Studies of brain chemistry and of mechanisms of action of antidepressant medications continue to inform the development of new and better medical and psychotherapy treatments. "STAR* D", a large study funded by the National Institutes for Mental Health, found that less than half of patients got completely well after a single antidepressant was taken, and although more patients got well once they were switched to another medicine, the proportion of those who got better decreased each time a person had to switch to another medication[1].

Recent advances in treatment have occurred for patients with mood disorders, these include: pharmacotherapy, combined psychotherapy pharmacotherapy, and novel physical therapies. The focus of new drug development reflects a shift from serotonin specificity to combine or specific noradrenergic activity. The efficacy of sequencing cognitive therapy after anti-depressant treatment in patients who were partially remitted was examined recently by Paykel and colleagues. The cumulative relapse rate was reduced significantly from 47% in the clinical management control group to 29% in the group that received 16 sessions of cognitive therapy.

Improved recognition, treatment, and prevention of depression are critical public health priorities. Recent years have been associated with significant advances in the understanding of depressive disorders with reflections on the nature and quality of care offered to the depressed patient. These advances occurred in perspectives of neurobiology of depression at neuroanatomical and neuro- molecular levels. The objective of this paper is to highlight recent developments in the neurobiology and treatment of depression.

Prevalence of depressive disorders

Epidemiological studies have consistently shown that depression is one of the most prevalent lifetime psychiatric disorder, and that major depressive disorder (MDD) remains one of the most frequently seen psychiatric illnesses in primary care settings[2]. Lifetime prevalence varies widely, from 3% in Japan to 17% in the US. In most countries the number of people who would suffer from depression during their lives falls within an 8–12% range[3,4]. The Iraqi Mental Health survey reported a lifetime prevalence of 7.82% [5]. Population studies have consistently shown major depression to be about twice as common in women as in men, although it is unclear why this is so, and whether factors unaccounted for are contributing to this. People are most likely to suffer their first depressive episode between the ages of 30 and 40, and there is a second, smaller peak of incidence between ages 50 and 60[6]. The risk of major depression is increased with neurological conditions such as stroke, Parkinson's disease or multiple sclerosis, and during the first year after childbirth[7]. It is also more common after cardiovascular illnesses, and is related more to a poor outcome than to a better one [8,9].

Course of depressive disorders

MDD is a recurrent episodic disorder. In a 15-year follow up of a prospective study of a sample of 380 patients with MDD episode, 73% experienced a recurrent episode[10]. Each subsequent episode increases the probability of further episodes[11]. The STAR*D project revealed that 74% of 1500 patients treated experienced more than one episode [1].

Several factors are thought to contribute for the neurobiological vulnerabilities underlying recurrence of MDD, these include:

- Family history of depressive illness and an earlier onset of first episode[1].
- The process of "kindling", in which the threshold for the impact of stressful life events becomes lowered[12].
- Number of previous episodes of MDD[13].
- High genetic loading[14] .
- Early childhood adversities[15] .
- Neurobiological changes associated with depressive illness [1].

Recovery from depression is determined by the duration of the depressive episode. Patients whose depressive episodes persisted for more than 5 years experienced much lower recovery rate than patients whose episodes lasted less than one year[16, 17]. Thus, the golden treatment goal has been shifted from response to remission and recovery.

Recent developments in the neurobiology of depression

Advances in neuroimaging and other techniques, and diagnostic aids facilitated understanding neuroanatomical and functional change underlying depressive disorders. Abnormalities in many prefrontal and limbic structures, and their interconnected circuits have been associated with mood regulation; these include: the ventromedial prefrontal cortex (VMPFC), lateral orbital prefrontal cortex (LOPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulated cortex (ACC), ventral striatum plus nucleus accumbens (nAC), amygdala and hippocampus. These structures function as an integrated circuit implicated, in addition to mood regulation, in learning, memory, pain mediation, aggression, sexual function, eating behaviour, risk assessment, modulation of of maladaptive and preservative affective states, maintenance of executive functions, effortful sustained attention and working memory processes[18].

Regional blood-flow studies showed hyperactivity in the VMPFC and LOPFC (associated with increased sensitivity to pain, anxiety, depressive ruminations and tension) and hypoactivity in the DLFPC (associated with psychomotor retardation, apathy, and deficits in working memory and attention).

A decrement in the communication between the amygdala and ACC region was found in fMRI studies of neuroconnectivity, consequently this abnormality lead to a failure of the inhibitory function of the ACC on emotional regulation and further motivational and affective disruption[19,20].

The hippocampal volume was found to be reduced in patients (with greater decrement in the right hippocampal volume) in patients with MDD in imaging studies[21] . Genomic imaging studies have shown associations between hippocampal volume and specific genes that are mediated in mood disorders[22,23]. Moreover, morphological differences in the hippocampus may be a predisposing factor in MDD; however, structural changes can also accumulate in the course of the disease and thereby create an obstacle to full recovery.

The key findings at the neuromolecular level include:

1. Cortisol (stress hormone) has been found consistently elevated resulting in impairment in neuroplasticity and cellular resistance[24].
2. Imbalance between glucocorticoid and mineralcorticoid receptors in MDD resulting in neuronal damage in the hippocampus[25].
3. Stress results in release of glucocorticoids and corticotrophin releasing hormones (CRH), and proinflammatory cytokines. Depression disrupts serotonin, norepinephrine and dopamine leading to impairment in the regulatory feedback loops that "turn off" the stress response. Sympathetic activity contributes to immune activation and release of proinflammatory cytokines. The latter further interfere with monoaminergic and neurotrophic signaling and may diminish central corticosteroid receptor sensitivity leading to disruption of feedback control [26].
4. Levels of BDNF (Brain derived neurotrophic factor) have been found to be significantly lower in untreated patients with MDD compared with treated patients or healthy controls [27]. BDNF is a dendritic protein involved in cell maintenance, plasticity, growth and death. When BDNF interacts with tyrosine receptors kinase receptors, it promotes cellular resilience and long-term potentiation. BDNF dysregulation occurs under conditions of chronic stress and depression.
5. The "neurotrophic hypothesis" of the pathogenesis of major depression states that stress and genetic vulnerability elevate glucocorticoid steroids and alter cellular plasticity via down regulation of growth factors and receptor sensitivity [28]. The reduction in growth factors such as BDNF, impacts negatively on the structural and functional processes within the limbic system, especially the hippocampus. Furthermore, chronic and recurrent MDD may result in subsequent atrophy and further disruption in neuro circuity. The implication of this hypothesis, recovery and remission of MDD would be dependent

upon a reversal of these processes, such as increase in BDNF levels.

6. Recent findings from research on the monoamine theory revealed that chronic treatment with monoamine reuptake inhibitors increases activation of cyclic adenosine 3-4 monophosphatase (cAMP) which in turn stimulates protein kinase A; activation of this protein enzyme regulates target genes leading to an increase in BDNF synthesis[29]. Moreover, response to antidepressants has been associated with re-establishment of cortical activity and normalization in the amygdala and ACC, and failure in response was associated with elevation of proinflammatory cytokines[30,31,32]. Restoration of the neurobiological regulation in MDD via neurotrophic factors and neurogenesis appears to be a common factor across various effective treatments for MDD, including pharmacological, psychological and somatic treatments, such as diet and exercise [33].

Treatment of the depressed patient

The neurobiological hypothesis has several implications, these include:

1. Treatment intervention of MDD should be started early and focused on achieving rapid remission and recovery. Longitudinal studies have shown that one of the best predictors of remission status at 2 years was response to acute treatment, i.e. initial 6 weeks [34,35].
2. Early response to treatment can be augmented by the use of therapeutic interventions which activates multiple aminergic systems. Amongst these interventions is the use of combination treatments or dual reuptake inhibitors [36].
3. Dual reuptake inhibitors targeting both serotonin and norepinephrine had been shown to be associated with improving not only the core features of depression, but also the correlated physical symptoms, such as pain. These symptoms increase the illness burden and impair the ability to attain remission [37,38]. Patients with MDD who experienced more than 50% remission in pain were more likely to achieve remission than patients whose pain reduction was less than 50% [39]. Furthermore, patients who had attained partial remission were more likely to relapse (67.5%) than patients who had obtained full remission [40].

CONCLUSIONS

Major depression is a common mood disorder that affects a substantial number of people in any population. Neurobiological abnormalities underlie both the manifestations and disease burden of MDD. Recurrence and chronicity of MDD negatively impact the course of the disorder and outcome of treatment. The administration of combination of treatment interventions and dual reuptake inhibitors are likely to ensure early response and prevention of relapse. Recovery of function ought to be the target of any treatment plan.

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