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CURRENT MANAEGMENT ON DEPRESSION: AREVIEW

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ABSTRACT: The relationships between immune and neural function are an increasingly important area of study for neuropsychiatric disorders, in particular depression. This review summarizes the current theories and novel treatment strategies for depression, with a focus on cytokine-induced depression. The current diagnostic categories for depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders, however, are not etiologically or biologically derived, and it has been proposed that "depression", likely reflects multiple pathogeneses leading to varying symptom constellations. The mechanisms of action of antidepressants are not fully understood; the hypothesis that reversing hippocampal cell loss in depression may be their active principle is a fascinating new development. Moral panic about the claim that antidepressant serotonin reuptake inhibitors cause patients to commit suicide and become addicted to their medication may have disconcerted the public and members of the medical profession. We will try to describe the considerable effort that has gone into collecting evidence to enlighten this debate.

Key words: cytokine, hippocampa, constellations, neuropsychiat.

INTRODUCTION:

Compared with other medical diagnoses, depression is very common. It occurs twice as frequently in women as in men, can begin at any age, but has its average age of onset in the mid-20s.[1] Lifetime prevalence estimates for major depressive disorder (panel) in the community range from 15% to 17% (95% CI), 12-month prevalence from 6% to 7% (US national comorbidity replication; n=9090).[2,3] Major depressive disorder impairs the ability to function, leading to role impairment in well over 50 % of patients.[2] Role impairment is likely to be a direct corollary of depressed mood.[4,5] Effective treatment is therefore of the essence. Unfortunately, only 46–57% (95% CI) of the 12-month cases in the USA were receiving health care treatment for major depressive disorder, and only 18–25% were adequately treated.[2] In a European community survey (n=5993), 25–38% of men and 21–30% of women interviewed and classi.ed as having major depressive disorder used any health services in the past 12 months for their depression. This percentage rose to only 35–49% of those with severe major depressive disorder.[6] Any discussion of the epidemic rise in prescriptions of antidepressants together with popular scepticism towards antidepressant treatments has to be considered against this background Depression is especially common in many non-psychiatric medical settings, such as inpatients wards, in chronically ill patients and during the recovery from acute medical illness.[7] A crucial aspect of the epidemiology of major depression is the increased mortality associated with this condition. A recent meta-analysis of 25 studies with 1·3–16 years' follow-up of over 100 000 individuals reported an overall relative risk of dying between 1·58 and 2·07 (95% CI) compared with people who are not depressed.[8] The relative risk in subclinical depression was not substantially smaller than in clinical depression.The analysis did not examine potential confounders, such as chronic illness or lifestyle.The mechanism of increased mortality is therefore not clear. A major contribution to increased mortality in depression will come from the risk of suicide in this patient group. Traditionally, lifetime risk (ie, proportionate mortality: the percentage of the dead who died by suicide during follow-up) is reported between 15% and 19%.[9,10] This .gure is likely to be in.ated, especially if the period of follow-up, typically after an acute episode in hospital, carries a higher risk of suicide than periods further removed from the index episode.[11]

Another modifying factor is the diagnostic system: early versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), for example, drew the boundaries of depression much narrower than DSM III or IV, which include many milder forms of the illness. A recent review11 took account of the treatment setting of patients and identified a clear hierarchy of risks, with estimates of lifetime prevalence of suicide being highest in suicidal inpatients (8·6%), lower in other inpatients (4%), and lowest amongst outpatients with affective disorder (2·2%). Even with these revised the risk of suicide rises over background levels from four-fold in depressed outpatients to 16-fold in patients with affective disorders admitted because of suicidal risk.[11] A sixth of people in the community will have major depressive disorder during their lifetime. Only between a quarter and half of patients will be in contact with the health services for their depression. In half the cases, the illness is incapacitating, leading to role impairment at work or at home. The risk of premature death is increased, in part because of a greater risk of suicide.

Physical treatments in depression

Transcranial magnetic stimulation has recently received much publicity, both as an interesting method to investigate neuronal function in vivo in humans and as a potential treatment method to supplement or even to replace drug treatment and electroconvulsive treatment in depression[12]It has great potential as a noninvasive investigative method, especially if combined with imaging methods. Transcranial magnetic stimulation is able to disturb neuronal activity in a way that allows for the examination of causality, rather than generating associations, as most imaging methods do. Combined with neuroimaging, the spatial distribution of such stimulated neuronal networks can be mapped. After initial enthusiasm about its treatment potential, the current assessment is more sober. The forest plot of controlled trials in depression indicates a secular trend with more recent trials showing smaller effect sizes[12-41] experimental treatment modality.

Electroconvulsive therapy

Despite public and professional misgivings, ECT remains the most effective treatment for depression; especially if it presents with psychotic symptoms, such as delusions and hallucinations.[42-43] Apart from therisk of general anaesthetic, the main objection to ECT has been its liability to cause memory impairment. Research on cognitive functioning after ECT has been far from comprehensive and is complicated by the improvement of cognition due to the alleviation of depressive symptoms. A recent robust study examined the effects of ECT on episodic memory and noted that the anterograde amnesic effects of ECT were greater for knowledge about the world ie, impersonal memory, than for autobiographical memory—ie, personal memory. In a systematic review and metaanalysis[42] the UK ECT Review Group stated that data relating to cognitive functioning after ECT were not complete, but the tentative conclusion could be drawn that cognitive impairment consisted mostly of temporary anterograde and retrograde amnesia[42] Furthermore, the method of ECT used in the treatment of depression was linked to the degree of cognitive impairment produced. For example, bilateral ECT produces greater impairment than unilateral ECT, and higher energy treatment produces greater impairment than lower energy. The effects of ECT are short-lived so patients are likely to require follow-on pharmacological therapy.Further research into the long-term cognitive effects of ECT is recommended as there is a dearth of randomised controlled trials researching this area.The role of neurosurgery in the management of patients highly resistant to treatment and its invasive nature make future randomised controlled studies unlikely. Vagal nerve stimulation has been proposed as a treatment in drug-resistant and ECT-resistant depressed patients, but the evidence for it effectiveness is as yet inconclusive.[43] Deep brain stimulation as a currently experimental treatment might offer an intervention similar to neurosurgery,which is both reversible and amenable to withinparticipant placebo control. Six patients with severe refractory depressive disorder, who had failed to respond to antidepressant, psychotherapeutic, and electroconvulsive therapies were treated in an open study, in which electrodes were implanted in the white matter tracts immediately lateral to the subgenual anterior cingulate.[44] Striking and sustained remission of depression was reported in four of the six patients.

Furthermore, PET images showed a pronounced reduction in locally abnormally increased subgenual cerebral metabolism, as well as changes in downstream cortical and limbic sites. The authors[44] concluded that disrupting focal pathological activity in the subgenual region using deep brain stimulation could effectively reverse symptoms in depression that is otherwise resistant to treatment. Other recent studies have reported the results of deep brain stimulation for refractory obsessivecompulsive and anxiety disorders. Based on studies of internal capsulotomy for these disorders, four patients with treatment refractory severe obsessivecompulsive disorder were reported in an open study. The patients had electrodes implanted in the anterior limbs of the internal capsule. This stimulation had beneficial effects in three patients, with one having an especially striking result. For this one patient, the investigators then did a double-blind trial with video assessment and six independent assessors. The findings of the more rigorous double-blind assessment supported the conclusions of the initial less detailed open study assessment; during deep brain stimulation the patient had a pronounced increase in ratings of social contact, communication, .ow of ideas, assertiveness and mobility, a decrease in doubt, and no change in sustained attention. On the basis of this and other work, an open study investigated treatment of refractory obsessivecompulsive disorder and anxiety disorders with deep brain stimulation of the anatomically adjacent shell of the nucleus accumbens.[45] A good reduction in symptom severity was reported in three of four patients. Additionally,PET images of one patient during stimulation showed a change in brain metabolism as a result of the stimulation. Two distinct issues remain to be determined from such work: treatment effectiveness and treatment mechanism. Determination of treatment effectiveness should take no account of theories of mechanism, but should instead use the accepted methods of evidencebased medicine. The need for evidence-based medicine in assessing neurosurgery for mental disorders has long been recognised. However, there are considerable practical dif.culties in implementing evidence-based medicine methods in a treatment of last resort, for which very few patients, even worldwide, are judged suitable. There are no prospective randomised double-blind placebocontrolled trials of any procedure, and none is likely.[46]

In the case of deep brain stimulation however, the publication of a double-blind trial188 in a single patientis encouraging for future studies of stimulation
effectiveness.

TMS- Transcranial Magnetic Stimulation

This is a relatively new and still experimental procedure that is not yet approved by the FDA for treating Depression. It is done by a physician who has a magnetic coil that receives pulses of electric current. The magnetic coil is passed over the scalp and the electric pulses penetrate the bones of the skull to stimulate the nerve cells of the brain.[47] Though this procedure is still considered experimental many hospitals and clinics offer it.

Cytokines in the central nervous system

Cytokines in the central nervous system: 1) are constitutively expressed, 2) can have functions such as neuroprotection or neurodegeneration, and 3) can be regulated by nonimmune factors, such as neurotransmitters and hormones. Peripheral cytokines can also access the brain and affect function via vagal nerve activation, a leaky or compromised blood–brain barrier, and active transport across the blood–brain barrier, or binding to cell-surface proteins on brain endothelial cells. The most recent finding in this area support and extend these concepts by showing that during an immune and in.ammatory response, acute activation of tumor necrosis factoralpha (TNF-á) leads to chronic increases in brain levels of proin-.ammatory cytokines administration of IFNactivates expression of several IFN-stimulated genes in brain as well as in peripheral organs exposure to a psychosocial stressor, greatly augments the effects of immune activation on sickness, plasma corticosterone and hippocampal norepinephrine, as well as on the levels of circulating IL-6, TNF-á and IL-10 [48]IFN-ã participates in the death of dopaminergic neurons by regulating microglial activity thus, IFN-ã induced activation of microglia and consequentneuronal loss may contribute to the modulatory effects of cytokines on depressive symptoms. Collectively, this body of research has led investigators in the field to appreciate that hyperactivation of the immune system and associated signaling cascades results in increased levels of proin.ammatory cytokines accompanied by glucocorticoid and immune system dysregulation and deleterious neuropsychiatric effects (e.g., depression).

In addition to studying the up-regulation of in.ammatory molecules, such as TNF-á or IL-1â, further research to identify and investigate the role of proteins not increased or downregulated during an immune challenge may contribute towards a better understanding of the pathways and molecular targets involved in cytokine-induced depression.

Mechanisms of cytokine-induced depression

Cytokines play an active role in the molecular events in.uencing synaptic transmission, neuronal plasticity, and depressive behaviors. However, although cytokine-induced depression is well-established, the specific mechanisms by which activation of the innate immune system and expression of species depressive symptoms are related remain poorly understood, in part, because of the complex and diverse processes involved. The potential mechanisms leading to cytokine-induced depression are numerous and were recently reviewed by and others. Included among these mechanisms are several lines of evidence demonstrating how cytokines can contribute to HPA axis hyperactivity as well as affect the serotonergic and dopaminergic systems and subsequently lead to depressive symptomatology. There is, however, a need for a more integrated view of depression. Given that in humans as well as in animal models of depression treatment with cytokines produces depressive symptoms and that depression occurs more frequently in those with medical conditions, cytokines and other in.ammatory molecules may function as mediators of depressive symptoms. Currently, there is not a consensus in the literature regarding the role of the immune system and in.ammatory pathways on the etiology of depression. In fact, it is still debated whether or not in.ammatory responses occur in brain summarizes the putative psychoneuroimmunological factors and biochemical correlates associated with depression.

Novel treatment strategies

The use of anti-in.ammatory approaches for the treatment of depression is being examined at both pre-clinical and clinical levels. Many antidepressant medications have speci.c anti-inflammatory effects and significant immunoregulatory activities, such as reducing the number of Th1 cells secreting IFN-ã [48]increasing the production of IL-6 and IL-10 and inhibiting IFN-γ-induced microglial production of IL-6 and nitric oxide Increasing evidence suggests that antidepressants operate in part to repair neurotransmission by enhancing neurogenesis as well as axonal and dendritic sprouting However, current pharmacologic approaches are effective in less than 50% of patients.and immune activation in patients with depression is also associated with resistance to treatment with traditional antidepressant medications. For example, (1) depressed patients non-responsive to drug treatment have increased immunity shown by elevated CD4+ T-cell activity and proinflammatory cytokine expression (2) suppression of IL-6 and TNF-α does not occur in depressed patients who fail to respond to antidepressants and (3) higher levels of TNF-α in patients with depression might predict a non-response to treatment with selective serotonin reuptake inhibitors (SSRIs)

Monoamines in the treatment of depression

Several lines of evidence indicate that an enhancement of 5-HT neurotransmission might underlie the therapeutic response to different types of antidepressant treatments[49] Two series of clinical observations have produced convincing results in support of this notion:(1) All selective 5-HT (serotonin) reuptake inhibitors (SSRIs) thus far tested have been found to be effective in major depression 6. Since most.of these drugs belong to different chemical families and the only common property they share is their capacity to inhibit the 5-HT reuptake carrier, it is indisputable that they exert their therapeutic effect primarily via the 5-HT system. (2) Inhibition of 5-HT synthesis in drug-remitted depressed patients, using the tryptophan hydroxylase inhibitor para-chloro-phenylalanine 7,s and, more recently, the tryptophan-depletion paradigm under rigorous controlled conditions, produced a rapid relapse of depression. It is important to underscore that, for each patient, the symptomatology reactivated by the depletion was nearly identical to that present before the response to the antidepressant treatment.

SSRIs

It appears paradoxical that SSRIs inhibit the 5-HT transporter within minutes whereas they exert their full antidepressant effect only after a few weeks of treatment. This clearly indicates that reuptake inhibition per se is not responsible for the antidepressant response, but rather that adaptative changes underlie their therapeutic effect.

In an attempt to resolve this discrepancy, the firing activity of 5-HT-containing neurones was determined in rats during SSRI treatment, because this parameter is of major importance in controlling 5-HT release in postsynaptic brain regions. A two-day treatment with different SSRIs markedly attenuated firing activity of 5-HT-con- taining neurones. However, these neurones progressively regained their normal firing activity during a two-week treatment. 5-HT-containing neurones are endowed with somatodendritic 5-HT1A autoreceptors, which exert a negative feedback influence on their firing activity Therefore; the sensitivity of the autoreceptors was assessed to explain the recovery of the firing activity of 5-HT-containing neurones during prolonged SSRI treatment. The suppressant effect of i.v. administered lysergic acid diethylamide (LSD; an agonist at somatodendritic 5-HT autoreceptors), as well as that of direct microiontophoretic application of 5-HT and LSD onto 5-HT-containing neurones, was attenuated following 14-day treatments with SSRIs. Therefore, normal firing activity of 5-HT-containing neurones is restored as a consequence of somatodendritic 5-HT1A autoreceptor desensitization. This might explain, at least in part, the delayed onset of action of SSRIs in major depression. It would indeed be difficult to imagine that 5-HT-mediated transmission could be markedly increased by carrier blockade when 5-HT-containing neurones are who showed that acute administration of an SSRI produced a small and transient increase in extracellular 5-HT concentrations in the rat frontal cortex, as measured by in vivo microdialysis, whereas continuous infusion of a clinically relevant dose of the same SSRI for 14 days resulted in a sixfold increase in extracellular 5-HT concentrations·

Monoamine oxidase inhibitors

Drugs that inhibit the A form of monoamine oxidase (MAO) are effective antidepressants while selective inhibition of MAO-B has no therapeutic effect in major depression MAO-A inhibitors, as is the case for SSRIs, produce an initial decrease in the firing activity of 5-HT- containing neurones, which is followed by a progressive recovery during a three-week treatment The recovery is also due to the desensitization of somatodendritic 5-HT1A autoreceptors. However, this cannot account for the enhancement of 5-HT-mediated transmission observed after a 21-day treatment. Indeed, when MAO is acutely inhibited and the 5-HT-mediated pathway is electrically stimulated, a prolongation of the suppression of firing activity of hippocampal pyramidal neurones is not produced TM. Consequently, inhibition of MAO-A per se does not enhance 5-HT release. Furthermore, long-term administration of MAO inhibitors does not desensitize terminal 5-HT autoreceptors TM.

5-HT1A receptor agonists

The selective 5-HT1A receptor agonists buspirone and gepirone were initially shown to exert an anxiolytic effect in humans [5051] and, subsequently, to have antidepressant properties in placebo-controlled clinical trials although buspirone is generally considered to be less efficacious than classical antidepressant drugs. 5-HTlA receptors are located both on the cell body of 5-HT-containing neurones, where they control firing activity, and on post-synaptic neurones, with a particularly high density in limbic structures. Acute and short-term administrations of 5-HTIA receptor.~gonists produce a suppression of firing of 5-HT-containing neurones, which results in a decreased 5-HT release in projection areas (However, during sustained treatment, activity of 5-HTcontaining neurones progressively returns to normal as a result of a desensitization of the somatodendritic 5-HT1A

Autoreceptors The gradual recovery of activity of 5-HT-containing neurones is consistent with the delayed onset of clinical action of these drugs. Interestingly, the postsynaptic 5-HT 1A receptors in the hippocampus do notdesensitize as do their presynaptic congener.

Tricyclic antidepressant drugs

Unlike the three classes of drugs discussed above, tricyclic antidepressant drugs do not modify the function of 5-HT-containing neurones, with the exception of clomipramine, which is the most potent 5-HT reuptake inhibitor of the tricyclic antidepressant drugs.

Various classes of tricyclic antidepressant drugs (that inhibit the reuptake of either 5s-HT or noradrenaline, neither of these, or both) have been shown to progressively sensitize postsynaptic 5-HT receptors in the hippocampus 31. This neuronal response was later shown to be mediated by the 5-HT1A receptor subtype

Conclusion:

This review summarized current theories regarding the relationships between immune activation and neural function, as they relate to the development and expression of depressive symptoms. Collectively, this body of clinical and pre-clinical research supports the theory that inflammation and immune dysregulation can influence neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and growth factor production, thus altering neural circuitry and contributing to depressive symptomatology. The current diagnostic categories for depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders, however, are not etiologically or biologically derived, and it suggested that "depression" reflects multiple pathogeneses leading to varying symptom constellations

Depression is not only a very common, incapacitating, and occasionally lethal illness that deserves our full attention, but also spans a wide range of severity andrequires a large choice of treatments. It is common in non-psychiatric medical settings and crucially affects presentation with physical illness and recovery from such illness. All effective treatments for this condition, which is by its very nature associated with the most profound suffering

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