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Restoring Balance to the Recently Disputed Chemical Imbalance Theory of Depression

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Depression is a common clinical presentation in patients of all ages with a worldwide prevalence of 5%. [1] It represents a major public health concern, contributing significantly to disability, morbidity, mortality, and adverse economic impacts. The World Health Organisation has predicted it will become the leading cause of disability by 2030[1]. Rates of depression in adolescents are increasing at a greater rate than in adults, with a 12-month prevalence of 7.5% among US adolescents[2]. The Growing up in Ireland (GUI) study found rates of 16% at age 13[3]. Given the association of depression with suicide, known to be high among youth in Ireland, and the often chronic and recurring nature of the illness, early recognition and treatment is important.

The causes of depression are likely multifactorial, involving a complex interaction between social, psychological, and multiple biological factors, the import of each being different for each individual. Consequently, both treatment and prevention should be multifactorial, using a bio-psycho-social approach. Despite years of research, the biological contributions remain poorly understood and given the complexity of the brain, this is not unexpected.

Abnormalities in the serotonergic system, identified in the 1960s contributed to research into depression and supported by the effectiveness of the selective serotonin re-uptake inhibitors (SSRIs) was offered as a plausible theory[4]. In short, this hypothesis proposes that depression is due to lowered levels or activity of serotonin. Whilst this hypothesis dominated research into the pathophysiology and pharmacotherapy of depression, it was acknowledged to be inadequate, over simplified and but one plausible explanation.

A rigorously conducted umbrella review examining the serotonin hypothesis of depression[5] has once again reminded us of the naivety of the assumption that depression is anything other than a heterogeneous group of disorders with multiple and interacting aetiologies. The authors found 'no convincing evidence that depression is associated with or caused by lower serotonin'.

Additional theories for depression exist especially in youth, such as attachment and interpersonal theories and must be considered. Equally depression in parents play a role via genetic and environmental factors. Abnormalities in the neuroendocrine system and the sleep-wake cycle, and sociocultural models might explain the rising rates of depression, especially amongst adolescents heavily influenced by social media. These theories also emphasize the basics of mood hygiene, such as healthy nutrition, exercise, and sleep. Given the widely distributed neuro-modulatory system it seems possible that even these alternative theories may be influenced by, or resultant from, neurochemical activity, including serotonin.

Following the umbrella review publication[5], Google Trends indicted that searches for 'serotonin 'and 'anti-depressants' hit the highest level to date. Some academic and social media discussions proposed the serotonin theory was promoted by aggressive and unethical marketing by pharmaceutical companies and supported by their unhealthy relationship with the psychiatry profession. Psychology Today referred to it as 'a multibillion dollar error' 'tied to a discredited theory that is still fueling mass prescribing on a global basis'[6]. Fellow psychiatrists and academics[7] stated 'the psychiatry profession acted as a willing and often enthusiastic conduit of the serotonin theory of depression 'and were responsible for 'propagating an unsupported theory and the mass use of antidepressant drugs'[7]. Pharmaceutical company influence of prescribing practice remains an important subject, especially in an era where prescribing rates continue to increase in all fields of medicine. Unhealthy and unethical relationships must be called out, but this must be balanced with concurrent recognition of the beneficial impact that pharmaceutical research has had on understanding of illness and alleviation of suffering.

Prescribing practice in psychiatry seems to be brought into dispute more often compared to other medical disciplines. Many medical conditions lack a robust aetiological theory yet their treatment with medication, also often without a clear mechanism of action, remains relatively unscrutinised, or at least not exposed to the same criticism as psychopharmacology. Take for example Paracetamol, the use of which is widely promoted and accepted despite its analgesic mechanisms not being completely understood.

Clinical message: A recent report suggests that rates of depressive episodes have increased by 27·6% following the COVID-19 pandemic[8]. The GUI Covid-19 study saw rates of 'low mood' in 12 years old increase to 22%. [9] This suggest it is likely that clinicians will continue to play a prominent role in supporting patients of all ages with depression. This will include consideration of the prescription of SSRIs based on the knowledge of their effectiveness and safety profile.

Although, some media reports suggest this umbrella review is evidence that SSRIs don't work, this is not stated by the authors[5] and evidence exists of effectiveness and acceptability of such medication even in youth[10]. The review paper and subsequent publicity may however lead to some adolescents and families being tempted to stop their medication. SSRIs are effective[10] and often lifesaving for many patients who take them, a position once again supported by the Royal College of Psychiatrists in response to the review paper. Clinicians are right to be reminded of the perils of a blind acceptance of any one theory, especially any offering simplistic explanations of causation for mental illnesses. It remains essential that clinicians remain open and curious about advances in the field of psychiatry and seek robust evidence for theory and practice. As always, the best approach remains a careful non-judgmental detailed assessment, examining potential adverse experiences or events that may contribute to the illness and benefit from a focus of treatment in their own right. Effective and appropriate use of psychotropic medication follows from an accurate diagnosis and occurs in the context of additional evidence-based therapeutic options.

The therapeutic alliance between doctor and patient is built on mutual trust and an assumption that the clinician is aware of the strengths and limitations of evidence, is open to support patients and their families in their choices of treatment, and is not unduly influenced by peer, organisation, commercial or media pressures. This excellent review article by Moncrieff and colleagues, functions to underline the importance of remaining true to the evidence, a message that might be inadvertently lost by anti-psychiatry sentiment contributing to a growing distrust of psychopharmacology and psychiatry practice more generally. If followed, many of our patients will suffer. Indeed, clinicians have an ethical, moral, and professional obligation to treat their patients experiencing depressive episodes with the best available evidence-based tools at their disposal whilst diligently monitoring for adverse sequelae and appropriately revising treatment components as necessary. Such tools include SSRIs and other pharmacological strategies employing serotonergic pathways.

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