Ir Med J; October 2022; Vol 115; No. 9; P669

October 20th, 2022

Serotonin, Depression, and Antidepressants

B.D. Kelly

Department of Psychiatry, Trinity College Dublin, Trinity Centre for Health Sciences, Ireland.

One person in eight lives with a mental disorder, according to the World Health Organization[1]. Anxiety and depressive disorders are the most common conditions. In 2019, 280 million people around the world were living with depression.

In Ireland, most cases of depression are treated in the community by general practitioners, primary care teams, and community mental health services. In addition, depressive disorders are the most common reason for admission to inpatient psychiatric units and hospitals, accounting for a quarter of admissions in 2020[2].

Treatment of depression should ideally follow a 'bio-psycho-social' approach. There are physical or 'biological' treatments (such as antidepressant medication), psychological treatments (such as cognitive behaviour therapy or CBT) and social interventions (reflecting the personal and social contexts in which depression develops and is managed). In an ideal world, all three elements of treatment are combined to reflect the circumstances and meet the needs of each individual[3].

Consistent with this model, the National Institute for Health, and Care Excellence (NICE) recommends a range of treatments for depression in adults, using a stepped care approach[4]. Among its recommendations, NICE endorses the use of selective serotonin reuptake inhibitor antidepressants (SSRIs) in certain common scenarios which are outlined in its guidelines.

While rates of prescription of antidepressants are difficult to identify with precision, one study shows that the number of medical card holders prescribed antidepressants in Ireland grew from 9.4 per 100 medical card holders in 2016 to 12.3 in 2020[5].

The causes of depression are not fully understood[6]. Multiple factors have potential roles, including changes in the hypothalamic-pituitary-adrenal axis, inflammation, neuroplasticity and neurogenesis, structural and functional brain changes, genes, epigenetic factors, and possible changes in monoamine neurotransmitters (serotonin, noradrenaline, dopamine), as well as life events and childhood adversity. There are varying levels of evidence to support links between each of these factors and risk of depression.

Potential links with serotonin have received particular attention owing to the clinical effectiveness of SSRIs. If boosting serotonin improves depression, does this mean that serotonin deficiency underlies the condition in the first place?

Moncrieff and colleagues recently published a 'systematic umbrella review of the evidence' to elucidate this issue[7]. This group examined 17 studies, comprising of 12 systematic reviews and meta-analyses, one collaborative meta-analysis, one meta-analysis of large cohort studies, one systematic review and narrative synthesis, one genetic association study, and one umbrella review. They concluded that the main areas of serotonin research do not provide consistent evidence of an association between serotonin and depression.

In light of the diversity of factors potentially linked with depression, and the general complexity of brain function, this conclusion does not come as a surprise. Depression, like most mental illnesses, is defined by symptoms rather than biological markers, so it is highly unlikely that the condition, as currently defined, will map onto any simple biological explanation, such as a deficiency in a single neurotransmitter.

Any biological dysfunction that is linked with depression is almost certainly dynamic, complex, and rooted in multiple neurotransmitters, as well as other alterations in brain function and, possibly, structure. The absence of a simple, direct link with serotonin is unsurprising. Depression and the human brain are vastly more complex than that.

In addition, it is a fallacy to imagine that apparent 'biological' causes of depression (e.g., purported anomalies in neurotransmitters) are entirely separate to 'social' causes (e.g., childhood adversity). For example, it seems probable that changes in the hypothalamic-pituitary-adrenal axis play a role in several mental illnesses, including depression[6,8]. This can be described in terms of biological stress or in terms of associated social stressors, but the 'biological' is not separate from the 'social' or the 'psychological' in this scenario. All three are integrated with each other and act as different languages rather than separate causes.
In terms of treating depression, the main point to note is that this recent review of purported links between depression and serotonin, although useful and interesting, does not impact on the evidence base for current management of depression. The use of SSRIs is based on their effectiveness in randomised controlled trials and clinical practice, not on theories regarding possible links between depression and serotonin[6,9,10]. Therefore, SSRIs should continue to be used as indicated in NICE guidelines.[4]

As ever, it is helpful to bear in mind other treatment options which can be used, rather than relying on medication alone. CBT, for example, focuses on developing cognitive strategies (i.e., strategies related to thinking patterns and habits) and behavioural strategies (i.e., strategies related to actions and behaviours) in order to re-frame depressive thoughts, enhance coping strategies, reduce symptoms, and promote recovery.

There is strong evidence that CBT is effective in the management of many cases of depression, anxiety disorders, panic, social phobia, and post-traumatic stress disorder. For some people with mild or moderate depression, the benefits of CBT can exceed those of antidepressant medication. Other treatment approaches include interpersonal psychotherapy and mindfulness-based interventions, as well as social support and peer-led initiatives[3].

Overall, SSRIs remain an important part of the treatment of many cases of depression, even if the biological basis of the condition remains unclear. Treatments are highly effective for many people. Hopefully, future advances in biological psychiatry will help to better explain this disorder and better inform further progress in care.

Corresponding Author:
B.D. Kelly
Department of Psychiatry,
Trinity College Dublin,
Trinity Centre for Health Sciences,
Tallaght University Hospital,
D24 NR0A,
Ireland.
E-Mail: brendan.kelly@tcd.ie

References:

1. World Health Organization. Mental Disorders. Geneva: World Health Organization, 2022 (https://www.who.int/news-room/fact-sheets/detail/mental-disorders) (accessed 15 October 2022).
2. Daly A, Craig S. HRB StatLink Series 5 - National Psychiatric In-patient Reporting System (NPIRS): Annual Report on the Activities of Irish Psychiatric Units and Hospitals 2020. Dublin: Health Research Board, 2021 (https://www.hrb.ie/publications/publication/activities-of-irish-psychiatric-units-and-hospitals-2020/returnPage/1/) (accessed 15 October 2022).
3. Kelly BD. In Search of Madness: A Psychiatrist's Travels Through the History of Mental Illness. Dublin: Gill Books, 2022.
4. National Institute for Health and Care Excellence. Depression in Adults: Treatment and Management. London: National Institute for Health and Care Excellence, 2022 (www.nice.org.uk/guidance/ng222) (accessed 15 October 2022).
5. McCool A, Lukas K, Hayes P, Kelly D. Antidepressant medication prescribing patterns in Irish general practice from 2016 to 2020 to assess for long-term use. Irish Journal of Medical Science 2021 (Epub ahead of print) (https://doi.org/10.1007/s11845-021-02833-7)
6. Malhi GS, Mann JJ. Depression. Lancet 2018; 392: 2299-312 (http://dx.doi.org/10.1016/S0140-6736(18)31948-2).

7. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular Psychiatry 2022 (Epub ahead of print) (https://doi.org/10.1038/s41380-022-01661-0).
8. Zorn JV, Schür RR, Boks MP, Kahn RS, Joëls M, Vinkers CH. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis. Psychoneuroendocrinology 2017; 77: 25-36 (https://doi.org/10.1016/j.psyneuen.2016.11.036).
9. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database of Systematic Reviews 2009; 3: CD007954 (https://doi.org/10.1002/14651858.CD007954).
10. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. British Journal of Psychiatry 2012; 200: 97-106 (https://doi.org/10.1192/bjp.bp.111.096594).