Serotonin and depression – a riposte to Moncrieff et al. (2022)

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In their recently published systematic "umbrella" review, Moncrieff and colleagues conclude that there is no consistent evidence that depression is caused by decreased serotonin activity in the central nervous system (CNS). However, this paper – which was extensively publicized and received a lot of attention on the social media – can cause misunderstandings, since the serotonin hypothesis of depression in its original form (i.e. reduced serotonin activity in the CNS = depression) formulated more than 50 years ago has been considered outdated for several decades. It has long been known that depression is a heterogeneous disorder not only genetically, clinically and biologically but also from a pharmacotherapeutic perspective. The decreased activity of serotonin, which undoubtedly plays an essential role in the pathogenesis of depression, is characteristic of only a subgroup of depressed subjects whose clinical picture is mostly dominated by intensified negative emotions, agitation, anxiety, insomnia, decreased appetite, self-blame and suicidality and these individuals are primarily responsive to SSRIs. By contrast, depression cases with reduced positive affects (characterized by anhedonia, anergia, inhibition and reduced cognitive functions) are mainly caused by a disturbance in the metabolism of dopamine and/or noradrenaline. These patients are primarily responsive to dual-action (e.g. SNRI) antidepressants. Results of serotonin and catecholamine (dopamine, noradrenaline) depletion studies also suggest that that the dysregulation of serotonin and dopamine/noradrenaline in the CNS is characteristic of different subgroups of depressed patients. In addition to the serotonergic, dopaminergic and noradrenergic systems, many other neurotransmitter systems (e.g. cholinergic, glutamatergic, GABAergic) and other mechanisms (e.g. neuroinflammation) have also been proven to play a role in the development of the disorder.
Knowledge of the data presented in our publication is important since the simplistic interpretation by Moncrieff et al. of the role of serotonin in the pathogenesis of depression may undermine confidence in SSRIs in many patients.
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In the Abstract of their recent and extensively publicised systematic 'umbrella' review (Moncrieff et al. 2022), the authors conclude that "The main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations". In the last paragraph of the Discussion section they broaden their sceptical stance and call into question the biochemical determination of depression. In our view, there are several critical questions which the paper does not address adequately. In addition, the public media prominence given to the paper's findings may have disastrous clinical consequences.

IS IT PLAUSIBLE THAT DEPRESSION HAS NOTHING TO DO WITH SEROTONIN IN LIGHT OF THE EXTENSIVE EVIDENCE THAT ALL ANTIDEPRESSANTS ACT (DIRECTLY OR INDIRECTLY) ON VARIOUS ELEMENTS OF THE SEROTONERGIC SYSTEM?

There is overwhelming evidence that antidepressants (ADs) are more effective than placebo in the treatment of adults with Major Depressive Disorder (MDD) and that the great majority of them have effects on one or more elements of the serotoninergic system (Goodwin and Jamison, 2007; Cipriani et al., 2018; Kennedy et al., 2016; Malhi et al., 2021). This is reflected in evidence-based treatment guidelines adopted and promulgated in many countries. We are not aware of any such treatment guidelines for MDD that do not recommend ADs as a treatment option, especially for patients with moderate or severe depression (Cipriani et al., 2018; Malhi et al., 2021; NICE 2022; Kennedy et al., 2016).

This combination of evidence suggests (though of course it does not prove) that there is an association between 'depression' and serotonin. In our view this hypothesis is not refuted by the negative findings of Moncrieff et al's umbrella review with regard to various specific markers of the activity of the serotonin system.

In this short paper we discuss the limitations of the Moncrieff et al. review and of the conclusions that can be drawn from it, as well as the potential adverse consequences that could arise if its conclusions are misinterpreted.

THE PATHOGENESIS AND CLINICAL PRESENTATION OF MDD ARE BOTH EXTREMELY COMPLEX. IT IS THEREFORE PLAUSIBLE THAT DISTURBANCES OF THE SEROTONIN SYSTEM ARE ONLY IMPLICATED IN A SUBGROUP OF DEPRESSED PATIENTS.

The conclusion of the Moncrieff paper makes the implicit (and unwarranted) assumption that 'depression' is a biologically/pharmacologically homogenous condition. The authors also imply that within the predominant current biological model of depression, serotonin is always involved in its pathogenesis. However, it has long been accepted that the pathogenesis of MDD is a complex process involving several interconnected elements including monoaminergic, cholinergic, GABAergic and glutamatergic systems, neurotrophic factors, inflammatory factors and the HPA axis (Goodwin and Jamison, 2007; Nutt et al., 2008; Lamers et al., 2013; Enkhuizen et al., 2015; Malhi et al., 2021; Stahl., 2019; 2021; Dulawa and Janowsky, 2019). It is illogical to expect that a specific dysregulation (such as underactivity of serotonin transmission) would be detectable in all or even in the majority of patients with depression. In keeping with this heterogeneity, the consistent finding from reviews and meta-analyses of treatment trials is that only about one-third of MDD patients show an excellent response (remission) to SSRI treatment (Jakobsen et al., 2017; Cipriani et a, 2018; Malhi et al., 2021), suggesting that serotonergic involvement is only predominant in a minority of patients with MDD.

There is also extensive evidence that, in addition to serotonin, other neurotransmitters (most obviously noradrenaline and dopamine) are also involved in MDD – especially in patients who tend to present with retardation, anhedonia and lack of motivation. This subgroup of depressed patients responds well to dual action (dopamine and noradrenaline reuptake inhibitor or serotonin and noradrenaline reuptake inhibitor) antidepressants (Jain, 2004; Goodwin and Jamison, 2007, Ruché et al., 2007, Nutt et al., 2008; Stahl, 2008, Dubinina et al., 2021; Malhi et al., 2021).

The conjecture that other neurotransmitter systems are also involved in the pathophysiology of depression in some patient subgroups is also supported by the fact that patients with melancholic depression respond better to broad-acting ADs (Boyce et al., 2020; Malhi et al., 2021). Moreover, the administration of broad-acting antidepressants (also involving noradrenergic,

dopaminergic and melatonergic mechanisms) results in higher overall response/remission rate than monotherapy with SSRIs (Jain, 2004; Thase et al., 2017; Papakostas et al., 2018; Stahl, 2019). There is also some evidence that switching SSRI non-responders to broad-acting ADs is frequently associated with good response to the new (second) medication (Papakostas et al., 2008; 2018; Kato et al., 2018; Boyce et al., 2020), though in some studies (e.g. in the STAR*D) inter-class switches were not more effective than intra-class switches (Gaynes et al., 2008, Boyce et al., 2020).

There is also evidence that induced impairment of serotonin function by tryptophan depletion can cause clinical depression in some people with recurrent depression in remission – particularly those with a 'serotonergic' clinical presentation (Goodwin and Jamison 2007; Ruhé et al., 2007; Cowen and Browning, 2015; Homan et al., 2015; Manchia et al., 2017; Dubinina et al., 2021).

Therefore, a key conceptual problem with this umbrella review is that Moncrieff et al. do not consider that 'depression' (more precisely MDD as defined within the third and subsequent editions of the Diagnostic and Statistical Manual of Mental Disorders) is a heterogeneous illness genetically, biologically, clinically and pharmacologically. These dimensions may exist in a variety of combinations. Both unipolar and bipolar depression could (for example) be familial and non-familial, early onset and late onset, suicidal and non-suicidal, agitated and retarded, seasonal and nonseasonal, atypical and melancholic, psychotic and nonpsychotic and SSRI-responsive and SSRI-nonresponsive. There may however be important 'clustering' between dimensions - early onset major depression for example being mostly familial, bipolar, seasonal and suicidal (Goodwin and Jamison, 2007; Lamers et al., 2013; Dubinina et al., 2021; Malhi et al., 2021).

Moncrieff et al. argue that tryptophan depletion studies do not result in depression-like symptoms in healthy people. In our view this conclusion is oversimplistic. Most of the studies cited look at mood effects over a very short period, whereas the mood effects of tryptophan depletion (and subsequent brain serotonin lowering) would be expected to take several days or a few weeks to become apparent in non-vulnerable individuals. The review also fails to mention the more appropriately designed studies which are of people with MDD and which show depressive relapse after tryptophan depletion only in SSRI responders/remitters, but not in patients responsive to noradrenegic/dopaminergic antidepressants. There is also evidence that responders to dopaminergic or noradrenergic antidepressants do not relapse after tryptophan depletion but do relapse after catecholamine depletion (Ruhé et al., 2007, Homan et al., 2015). This suggests that modification of serotonergic and monoaminergic neurotransmission is indeed implicated in the mode of action of antidepressants.

More fundamentally, it has been also found that among unmedicated patients with remitted depression, serotonin depletion induced significantly more depressed mood, sadness and hopelessness than catecholamine depletion, and catecholamine depletion resulted in more inactivity, concentration difficulties, lassitude and somatic anxiety. This suggests that serotonin and catecholamines have differential roles in the pathophysiology of depression (Homan et al., 2015). These studies provide further evidence both for the heterogeneity of MDD and for serotonergic involvement in its pathogenesis.

SEROTONIN AND OTHER NEUROTRANSMITTERS HAVE MAJOR EFFECTS BOTH WITHIN AND BEYOND DEPRESSION

The synthesis of basic, animal and human (clinical) studies (reviewed by Stahl (2002), Nutt et al. (2008) and Guzel and Mirowska-Guzel (2022)) indicates that serotonergic, noradrenergic and dopaminergic neurotransmitter systems contribute significantly to the regulation of several normal physical and psychological functions including blood pressure, pulse rate, sexuality, vigilance, appetite, bowel motility, motivation and sleep. They also have significant actions in relation to specific depressive symptoms.

Increased negative emotions (resulting in self-punishment-like behaviour) such as worthlessness, guilt, suicidal ideation, appetite and sleep-loss etc. are related to decreased central serotonin activity, while decreased positive affects like anhedonia, loss of interest, loss of motivation, fatigue, energy-loss, concentration difficulties are connected to lowered central dopaminergic function. Finally, stressful emotions (fear, anger, anxiety) relate to decreased central noradrenergic tone (Stahl, 2002; Nutt et al., 2008; Cowen, 2015; Homan et al., 2015; Wang et al., 2020). However, as the range of clinical presentations of major depressive episode shows, in the majority of cases more than one of these three neurotransmitters are involved. It is therefore clear that both serotonin and catecholamines (dopamine and noradrenaline) have roles in the pathophysiology of depression and

in the regulation of 'normal' emotions that become pathologically intense in clinical depression (Manchia et al., 2017; Dubinina et al., 2021; Malhi et al., 2021.

There is therefore no doubt that depression is more than serotonin dysfunction and that serotonin disturbance is associated with more than depressed mood. Independent of clinical diagnosis, central serotonin dysfunction is clearly related to aggression, impulsivity and suicide, symptoms frequently seen in major depression (Goodwin and Jamison, 2007; Mann, 2013, Cowen, 2015; Manchia et al., 2017; Dubinina et al., 2021). Such serotonin dysfunction may contribute to the aggressive, impulsive, suicidal clinical picture in some depressed patients.

DID THE UMBRELLA REVIEW COVER ALL IMPORTANT ASPECTS OF THE SEROTONINERGIC SYSTEM?

There is increasing recent evidence that disturbed serotonergic function is possible despite 'normal' levels of brain serotonin, if disharmony arises in the complex machinery of 5-HT1A and 5-HT2A heteroreceptor function (Borroto-Escuela et al., 2021). There is also emerging evidence that the influence of tryptophan and serotonin on mood and cognition relates importantly to the gut-brain axis (Jenkins et al., 2016; Guzel and Mirowska-Guzel, 2022). This makes the relationship between depression, tryptophan and serotonin yet more complex. This is illustrated in a recently published metaanalysis by Pu et al. (2021) who concluded that metabolic changes in peripheral blood were associated with MDD, with particular involvement of the tryptophan-5-HT-kynurenine pathway. This metaanalysis was omitted from the umbrella review by Moncrieff et al., even though plasma levels of tryptophan play an important role in the regulation of brain 5-HT synthesis. We also do not understand why some markers of serotonin dysfunction (such as decreased platelet imipramine binding and 5-HT uptake of platelets) that are considered to be reliable correlates of depression (Ellis and Salmond, 1994; Cowen, 2008) were omitted from the umbrella review.

More recently, it has been also found that the morphology of serotonin neurons produced from induced pluripotent stem cells of MDD patients differ between patients who were SSRI responders and those who were not. The longer neurites in SSRI non-responder patient-derived serotonergic neurons indicates that this cellular phenotype may be associated with SSRI treatment resistance (Vadodaria et al., 2019). This suggests that a better understanding of the role of serotonin in depression and antidepressant response will require the advanced techniques currently being developed in cellular neuroscience.

CONCLUSION

We have known for at least for 15 years that the serotonin hypothesis, in its original and most simplistic form (i.e. that low central serotonin is responsible for all depression) is inadequate. It has been modified and narrowed in recent decades, with our current understanding being that central serotonin dysfunction, or dysregulation of the central serotonin system (rather than simply lower central serotonin activity) is characteristic of only a subgroup of major depressives.

The review by Moncrieff et al. takes this oversimplistic hypothesis as their starting point and claims to disprove it. They do not however disprove the contention that serotonin plays a significant role in mood regulation, including aggression and impulsivity. The review's publication, and the discussion it has generated, are however helpful in reminding us that the role of serotonin in depressive disorders is complex and that our understanding of it remains incomplete.

Antidepressants have been in clinical use for 60 years, and SSRIs for 35 years. There is overwhelming evidence for their utility in the management of major depression – a complex, recurrent and hugely disabling disorder. There is also considerable evidence that different subgroups of depressed patients respond to antidepressants of different mechanism of action. Antidepressants do work, regardless of the fact that the exact biological basis of depressive disorders are as yet incompletely understood. The overgeneralisation and misinterpretation of the Moncrieff et al. review (which in our view provides an unsurprising answer to the wrong question) may cause depressed patients to stop their antidepressants for the wrong reasons and with potentially disastrous consequences. We would urge the authors to clarify this and to highlight the dangers.

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REFERENCES

1. Borroto-Escuela DO, Ambrogini P, Chruscicka B, Lindskog M, Crespo-Ramirez M, Hernández-Mondragón JC, Perez de la Mora M, Schellekens H. (2021). The role of central serotonin neurons and 5HT heteroreceptor complexes in the pathophysiology of depression: A historical perspective and future prospects. Int. J. Mol. Sci. 22:1927. https//doi.org/103390/ijms22041927
2. Boyce P, Hopwood M, Morris G, Hamilton A, Bassett D, Baune BT, Mulder R, Porter R, Parker G, Singh AB, Outhred T, Das P, Malhi GS. Switching antidepressants in the treatment of major depression: When, how and what to switch to? J Affect Disord. 2020; 261: 160-163.
3. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018; 391: 1357-1366.
4. Cowen PJ. Serotonin and depression: pathophysiological mechanism or marketing myth? Trends Pharmacol Sci. 2008;29: 433-6.
5. Cowen P.J., Browning M. (2015). What has serotonin to do with depression? World Psychiatry, 14: 158-160.
6. Dubinina E.E., Schedrina L.V., Mazo G.E. (2021)- Main biochemical aspects of the pathogenesis of depression. Part II. Neuroscience and Behavioral Physiology, 51: 1330-1343.
7. Dulawa SC, Janowsky DS. Cholinergic regulation of mood: from basic and clinical studies to emerging therapeutics. Mol Psychiatry. 2019; 24: 694-709.
8. Ellis PM, Salmond C. Is platelet imipramine binding reduced in depression? A meta-analysis. Biol Psychiatry. 1994; 36: 292-9.
9. Enkhuizen J van, Janowsky D.S., Olivier B, Minassian A, Perry W, Young J W, Geyer MA. (2015). The catecholaminergic-cholinergic balance hypothesis of bipolar disorder revisited. European Journal of Pharmacology, 753: 114-126.
10. Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M. The STAR*D study: treating depression in the real world. Cleve Clin J Med. 2008; 75: 57-66.
11. Goodwin FK. és Jamison KR. (2007): Manic Depressive Illness. Bipolar Disorders and Recurrent Depression. Oxford University Press, New York.
12. Guzel T, Mirowska-Guzel D. (2022). The role of serotonin neurotransmission in gastrointestinal tract and pharmacotherapy. Medicine, 2022, 27: 1680
https//doi.org/10.3390/molecule 27051680
13. Homan P, Neumeister A, Nugent A,C, Charney D.S, Drevets W. C, Hasler G. (2015). Serotonin versus catecholamine deficiency: Behavioral and neural effects of experimental depletion in remitted depression. Transl psychiatry, 5: e532: doi:10.1038/tp.2015.25
14. Jain R. (2004). Single-action versus dual-action antidepressants. Prim Care Companion Psychiatry, 8(Suppl.1) 7-11.
15. Jakobsen JC, Katakam KK, Schou A, Hellmuth SG, Stallknecht SE, Leth-Møller K, Iversen M, Banke MB, Petersen IJ, Klingenberg SL, Krogh J, Ebert SE, Timm A, Lindschou J, Gluud C. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. BMC Psychiatry. 2017; 17:.58.
16. Jenkins T. A., Nguyen J.C.D-, Polglaze K. E., Bertrand P.P. (2016). Influence of tryptophan and serotonin on mood and cognition with possible role of gut-brain axis. Nutrients, 8(1), 56;
https://doi.org/10.3390/nu8010056
17. Kato T, Furukawa TA, Mantani A, Kurata K, Kubouchi H, Hirota S, Sato H, Sugishita K, Chino B, Itoh K, Ikeda Y, Shinagawa Y, Kondo M, Okamoto Y, Fujita H, Suga M, Yasumoto S, Tsujino N, Inoue T, Fujise N, Akechi T, Yamada M, Shimodera S, Watanabe N, Inagaki M, Miki K, Ogawa Y, Takeshima N, Hayasaka Y, Tajika A, Shinohara K, Yonemoto N, Tanaka S, Zhou Q, Guyatt GH; SUN☺D Investigators. Optimising first- and second-line treatment strategies for untreated major depressive disorder - the SUN☺D study: a pragmatic, multi-centre, assessor-blinded randomised controlled trial. BMC Med. 2018; 16: 103.
18. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, Hasnain M, Jollant F, Levitt AJ, MacQueen GM, McInerney SJ, McIntosh D, Milev RV, Müller DJ, Parikh SV, Pearson NL, Ravindran AV, Uher R; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016; 61: 540-60.
19. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry. 2013; 18: 692-9.
20. Malhi GS, Bell E, Bassett D, Boyce P, Bryant R, Hazell P, Hopwood M, Lyndon B, Mulder R, Porter R, Singh AB, Mur5ray G. (2021). The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guideline for mood disorders. Australian and New Zealand Journal of Psychiatry, 55: 7-117.
21. Mann J.J. (2013). The serotonergic system in mood disorders and suicidal behavior. Phil Trans R Soc B, 368: 20120537.
http.//dx.doi.org/10.1098/rstb.20120537
22. Manchia M, Capriniello B, Valtorta F, Comai S. (2017). Serotonin dysfunction, aggressive behavior, and mental illness: Exploring the link using a dimensional approach. ACS Chemical Neuroscience, 8(5): 961-972.
23. Moncrieff J, Cooper R.E., Stockmann T, Amendola S, Hengartner M. P, Horowitz M.A. (2022). The serotonin theory of depression: A systematic umbrella review of the evidence. Molec Psychiatry, 20, July, 2022. https://doi.org/10.1038/s41380-022-01661-0
24. NICE (National Institute for Health and Care Excellence). Depression in adults: treatment and management. 2022.
25. Nutt D, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, Carrasco JL, Stahl S. (2008). The other face of depression, reduced positive affect: The role of catecholamines in causation and cure. Journal of Psychopharmacology, 21; 461-471-
26. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biol Psychiatry. 2008; 63: 699-704.

27. Papakostas GI, Nielsen RZ, Dragheim M, Tonnoir B, (2018). Efficacy and tolerability of vortioxetine versus agomelatine, categorited by previous treatment, in patients with major depressive disorder switched after an inadequate response. J Psychiatr Res, 101; 72-79.
28. Pu J, Liu Y, Zhang H, Tian L, Giu S. Yu Y. et al. (2021). An integrated meta-anlysis of peripherial blood metabolities and biological functions in major depressive disorder. Molec Psychiatry, 26: 4265-4276.
29. Ruhé H.G., Mason N.S, Schene A.H. (2007). Mood is indirectly related to serotonin, norepinephrine and dopamine level in humans. A meta.analysis of mooamine depletion studies. Molec psychiat, 12:331-359.
30. Stahl SM. The psychopharmacology of energy and fatigue. J Clin Psychiatry. 2002 Jan;63(1):7-8.
31. Stahl S.M. (2008). Essential Psychopharmacology Series. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 3rd ed. New York, NY, US: Cambridge University Press, 2008.
32. Stahl SM (2019). Dextromethorphan/Bupropion: A novel oral NMDA (N-methyl-d-asparate) receptor antagonist with multimodal activity. CNS Spectrums, 24, 461–466. doi:10.1017/S1092852919001470
33. Stahl, SM. Stahl's Essential Psychopharmacology Neuroscientific Basis and Practical Applications. Fifth Edition. Cambridge University Press, Cambridge, UK. 2021.
34. Thase ME, Danchenko N, Brignone M, Florea I, Diamand F, Jacobsen PL, Vieta E. (2017). Comparative evaluation of vortioxetine as with therapy in patients with major depressive disorder. European Neuropsychopharmacology, 27:773-781.
35. Vadodaria K.C., Ji Y, Skime M, Paquola A. C., Nelson T, Hall-Flavin D. et al. (2019). Altered serotonergic circuity in SSRI-resistant major depressive disorder patient-derived neurons. Molec Psychiat, 24: 808-818.
36. Wang F, Yang J, Pan F, Ho R. C, Huang J. H, (2020). Editorial: Neurotransmitters and emotions. Front Psychol 11:21. doi:10.3389/fpsyg.2020.00021

Szerotonin és depresszió - reakció Moncrieff és mtsai. (2022) tanulmányára

Moncrieff és mtsai. (2022) szisztematikus összefoglaló közleményükben arra a következtetése jutnak, hogy nincsenek meggyőző evidenciák arra nézve, hogy a „depressziót" a központi idegrendszer csökkent szerotonin aktivitása okozza. Ugyanakkor ez a – közösségi médiában is jól propagált és nagy figyelmet kapott – közlemény félreértésekre adhat okot, mivel a depressziók több mint 50 éve megfogalmazott szerotonin hipotézisét a maga eredeti formájában (csökkent központi idegrendszeri szerotoninaktivitás = depresszió) már több évtizede túlhaladottnak tekintjük. Régóta tudjuk, hogy a depresszió nemcsak genetikailag és klinikailag, hanem biológiailag és (farmako)terápiás vonatkozásban is heterogén betegség. A depressziók patogenezisében kétségtelenül fontos szerepet játszó szerotonin csökkent aktivitása csak egy depressziós alcsoportra jellemző, amelynek klinikai képét többnyire a felerősödött negatív érzelmek, az agitáció, a szorongás, az inszomnia, az étvágytalanság, az önvádlás és a szuicidális tendenciák dominálják, és ezek a betegek elsősorban SSRI-kra reagálnak. Ezzel szemben a csökkent pozitív affektusokkal járó (anhedóniás, anergiás és gátolt tünetekkel, illetve csökkent kognitív funkciókkal jellemezhető) depressziók esetében főleg a dopamin és/vagy a noradrenalin anyagcsere zavara áll fenn. Ezeknél a betegeknél elsősorban a kettős hatású (pl. SNRI) szerek hatékonyak. A szerotonin és katekolamin (dopamin, noradrenalin) depléciós vizsgálatok is igazolják, hogy a szerotonin és dopamin-noradrenalin központi idegrendszeri diszregulációja a depressziós betegek különböző alcsoportjaira jellemző. A szerotonerg, dopaminerg és noradrenerg rendszerek mellett számos egyéb neurotranszmitter (kolinerg, glutamáterg, GABAerg stb.) rendszernek és egyéb mechanizmusoknak (pl. neuroinflammáció) is igazoltan szerepe van a betegség kialakulásában.
A jelen közleményünkben közölt adatok ismerete azért is fontos, mert a szerotoninnak a depresszió patogenezisében betöltött szerepének a Moncrieff és mtsai. (2022) által adott leegyszerűsítő interpretálása sok betegben megingathatja az SSRI-kba vetett bizalmat.

Kulcsszavak: depresszió, szerotonin, dopamin, noradrenalin, SSRI, antidepresszívumok