



## BÖLÜM 18

### Antidepresanların Yan Etkileri

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#### GİRİŞ

Depresyon, dünya nüfusunun yaklaşık %8 – 12'sini etkiler ve dünya çapında yeti yitiminin önde gelen nedenidir (1). İlk depresyon atağının ardından, hastaların %22'si depresyona tekrar girmeye eğilimlidir. Bir yıl sonra semptomlar ve aktif tedaviye rağmen % 85'e kadar iki veya daha fazla atak gelişebilir. Daha uzun ve daha sık atak geçirmek, bekar olmak, düşük geliri ve yaşlı olmak prognozu daha kötüleştirir (2). Antidepresanlar, semptomların nüksetmesini önleyebilen etkili ve erişilebilir tedavi seçenekleridir. Orta ve şiddetli depresyonda veya diğer müdahalelere rağmen devam eden hafif veya eşik altı depresyonda birinci basamak tedavi seçenekleri olarak önerilmektedir. Bunun yansısı panik atak, travma sonrası stres bozukluğu, yaygınlaşmış anksiyete bozukluğu, obsesif kompulsif bozukluk ve bu hastalıkların eşlik ettiği diğer patolojilerde kullanılmaktadırlar (3).

#### ANTİ-DEPRESANLARIN ETKİ MEKANİZMASI

Mevcut tüm antidepresanlar, bir veya daha fazla monoaminin (*serotonin, nor-adrenalin, dopamin*) iletimini arttırmak yoluyla etkilerini gösterir. Bu

aşamadaki farklılıklar etki mekanizmalarından kaynaklanmaktadır. Günümüzde en yaygın olarak kullanılanlar sırasıyla selektif serotonin geri alım inhibitörleri (SSRI), serotonin ve noradrenalin geri alım inhibitörleri (SNRI), noradrenalin geri alım inhibitörleri (NRI) ve noradrenalin ve dopamin geri alım inhibitörleri (NDRI) şeklinde sıralanabilir (4 – 6). Serotonin, noradrenalin ve dopaminin parçalanmasını azaltan monoamino oksidaz inhibitörleri (MAOI) sayılabilir (6). Mir-tazapin, alfa2-adrenoreseptör negatif geri besleme yolunun etkisini azaltarak noradrenalin ve serotonin iletimini artıran bir presinaptik alfa2-adrenoreseptör antagonistidir (7). Agomelatin, melatonin tip 1 ve 2 reseptörlerinde bir agonist ve bir 5-HT2c antagonistidir. 5-HT2c blokajının hem noradrenalin hem de dopamin salınımını artırırken melatonin üzerindeki etkisinin sirkadiyen ritmi ve uyku kalitesini iyileştirdiği düşünülmektedir (8).

#### ANTİDEPRESANLARIN YAN ETKİLERİ

##### Antidepresanların Fiziksel Yan Etkileri

Antidepresan ilaçların seçimi her zaman hastanın tercihini, geçmiş deneyimlerini, önceki yanıtı ve herhangi bir eşzamanlı tıbbi komorbiditeyi veya

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## KAYNAKLAR

1. Seppala LJ, Wermelink AMAT, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG et al., Fall-risk-increasing drugs: a systematic review and meta-analysis: II. Psychotropics. *J Am Med Dir Assoc* (2018); 19(4)
2. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ*, 2018; 2;343:d4551.
3. Kok RM, Reynolds CF, Management of depression in older adults: a review. *JAMA*; 2017, 317(20):2114–2122
4. Kirsch I, Deacon B, Huedo-Medina T, et al. Initial Severity and antidepressant benefits: A meta-analysis of data submitted to the food and drug administration. *PLOS Med* 2008;5(2):e45. www.plosmedicine.org
5. Papakostas G, Perlis R, Scalia M, et al. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. *J Clin Psychopharm* 2006;26:56-60.
6. Geddes J, Carner S, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003;361:653-61.
7. Cipriani A, Furukawa T, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746-58.
8. Stahl S. Novel mechanism of antidepressant action: norepinephrine and dopamine disinhibition plus melatonergic agonism. *Int J Neuropsychopharm* 2007;10:575-8.
9. Diler RS, Avci A. Selective serotonin reuptake inhibitor discontinuation syndrome in children: six case reports. *Curr Ther Res* 2002;63:188–97.
10. van Geffen EC, Hugtenburg JG, Heerdink ER, van Hulten RP, Egberts AC. Discontinuation symptoms in users of selective serotonin reuptake inhibitors in clinical practice: tapering versus abrupt discontinuation. *Eur J Clin Pharmacol* 2005;61:303–07.
11. Emslie G, Kratochvil C, Vitiello B, et al. Treatment for Adolescents with Depression Study (TADS): Safety Results. *J Am Acad Child Adolesc Psychiatry* 2006;45:1440–55.
12. Emslie G, Kratochvil C, Vitiello B, et al. Treatment for Adolescents with Depression Study (TADS): Safety Results. *J Am Acad Child Adolesc Psychiatry* 2006;45:1440–55.
13. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 2008;359:2753–66.
14. Melvin GA, Tonge BJ, King NJ, et al. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry* 2006;45:1151–61.
15. Gordon M., Melvin G., Selective serotonin re-uptake inhibitors A review of the side effects in adolescents, *Australian Family Physician* Vol. 42, No. 9, september 2013
16. Voican CS, Corruble E, Naveau S, Perlemuter G: Antidepressant-induced liver injury: a review for clinicians. *Am J Psychiatry* 2014; 171: 404–415.
17. Chen M, Borlak J, Tong W: High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. *Hepatology* 2013; 58: 388–396
18. Fava M: Weight gain and antidepressants. *J Clin Psychiatry* 2000; 61(suppl 1):37–41.
19. Serretti A, Mandelli L: Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry* 2010; 71: 1259–1272.
20. Zimmermann U, Kraus T, Himmerich H, Schuld A, Pollmächer T: Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res* 2003; 37: 193–220.
21. Lee SH, Paz-Filho G, Mastronardi C, Licinio J, Wong ML: Is increased antidepressant exposure a contributory factor to the obesity pandemic? *Transl Psychiatry* 2016; 6:e759.
22. Kemp AH, Brunoni AR, Santos IS, Nunes MA, Dantas EM, Carvalho de Figueiredo R, Pereira AC, Ribeiro ALP, Mill JG, Andreão RV, Thayer JF, Benseñor IM, Lotufo PA: Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: an ELSA-Brasil cohort baseline study. *Am J Psychiatry* 2014; 171: 1328–1334.
23. Goldstein DJ: Duloxetine in the treatment of major depressive disorder. *Neuropsychiatr Dis Treat* 2007; 3: 193–209.
24. O'Regan C, Kenny RA, Cronin H, Finucane C, Kearney PM: Antidepressants strongly influence the relationship between depression and heart rate variability: findings from the Irish longitudinal study on ageing (TILDA). *Psychol Med* 2015; 45: 623–636.
25. Taylor CB: Depression, heart rate related variables and cardiovascular disease. *Int J Psychophysiol* 2010; 78: 80–88. 77
26. Schatzberg AF, Blier P, Culpepper L, Jain R, Papakostas GI, Thase ME: An overview of vortioxetine. *J Clin Psychiatry* 2014; 75: 1411– 1418.
27. Funk KA, Bostwick JR: A comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother* 2013; 47: 1330–1341.
28. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC: QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics* 2013; 54: 1–13.
29. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C, Detke MJ: Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. *J Clin Psychopharmacol* 2005; 25: 132–140.
30. Darowski A, Chambers SA, Chambers DJ: Antidepressants and falls in the elderly. *Drugs Aging* 2009; 26: 381–394.
31. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, Huffman JC: Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry* 2014; 75:e441–e449.

32. Kikuchi T, Uchida H, Suzuki T, Watanabe K, Kashima H: Patients' attitudes toward side effects of antidepressants: an internet survey. *Eur Arch Psychiatry Clin Neurosci* 2011; 261: 103–109.
33. Balon R, Segraves RT: Survey of treatment practices for sexual dysfunction(s) associated with anti-depressants. *J Sex Marital Ther* 2008; 34: 353–365.
34. Bella AJ, Shamloul R: Psychotropics and sexual dysfunction. *Cent Eur J Urol* 2013; 66: 466–471.
35. Reichenpfader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA, van Noord M, Lux L, Gaynes BN: Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. *Drug Saf* 2014; 37: 19–31.
36. Gartlehner GH, Hansen RA, Reichenpfader UK, Kaminski A, Kien C, Strobelberger MN, van Noord M, Thieda P, Thaler K, Gaynes B: Drug Class Review: Second-Generation Antidepressants: Final Update 5 Report. Drug Class Reviews. Portland, Oregon Health and Science University, 2011.
37. Montejo AL, Montejo L, Navarro-Cremades F: Sexual side-effects of antidepressant and antipsychotic drugs. *Curr Opin Psychiatry* 2015; 28: 418–423.
38. Rosenblat JD, Gregory JM, Carvalho AF, McIntyre RS: Depression and disturbed bone metabolism: a narrative review of the epidemiological findings and postulated mechanisms. *Curr Mol Med* 2016; 16: 165–178.
39. Cizza G, Primma S, Csako G: Depression as a risk factor for osteoporosis. *Trends Endocrinol Metab* 2009; 20: 367–373.
40. Wu Q, Bencaz AF, Hentz JG, Crowell MD: Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. *Osteoporos Int* 2012; 23: 365–375.
41. Vestergaard P, Rejnmark L, Mosekilde L: Selective serotonin reuptake inhibitors and other antidepressants and risk of fracture. *Calcif Tissue Int* 2008; 82: 92–101.
42. Andrade C, Sandarsh S, Chethan KB, Nagesh KS: Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry* 2010; 71: 1565–1575.
43. de Abajo FJ: Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging* 2011; 28: 345–367.
44. Haddad PM, Dursun SM: Neurological complications of psychiatric drugs: clinical features and management. *Hum Psychopharmacol* 2008; 23(suppl 1):15–26.
45. Hawthorne JM, Caley CF: Extrapyramidal reactions associated with serotonergic antidepressants. *Ann Pharmacother* 2015; 49: 1136–1152.
46. Schillevoort I, van Puijenbroek EP, de Boer A, Roos RAC, Jansen PAF, Leufkens HGM: Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case-control study using spontaneous reports. *Int Clin Psychopharmacol* 2002; 17: 75–79.
47. Madhusoodanan S, Alexeenko L, Sanders R, Brenner R: Extrapyramidal symptoms associated with antidepressants – a review of the literature and an analysis of spontaneous reports. *Ann Clin Psychiatry* 2010; 22: 148–156.
48. Hedenmalm K, Güzey C, Dahl M-L, Yue Q-Y, Spigset O: Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms. *J Clin Psychopharmacol* 2006; 26: 192–197.
49. Konstantakopoulos G, Kouzoupis AV, Papageorgiou SG, Oulis P: Putative neuroleptic malignant syndrome associated with sertraline withdrawal. *J Clin Psychopharmacol* 2009; 29: 300–301.
50. Boyer EW, Shannon M: The serotonin syndrome. *N Engl J Med* 2005; 352: 1112–1120. Iqbal MM, Basil MJ, Kaplan J, Iqbal MT: Overview of serotonin syndrome. *Ann Clin Psychiatry* 2012; 24: 310–318.
51. Isbister GK, Bowe SJ, Dawson A, Whyte IM: Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; 42: 277–285.
52. Ashton AK, Weinstein WL: Cyproheptadine for drug-induced sweating. *Am J Psychiatry* 2002; 159: 874–875.
53. Marcy TR, Britton ML: Antidepressant-induced sweating. *Ann Pharmacother* 2005; 39: 748–752.
54. Arfken CL, Joseph A, Sandhu GR, Roehrs T, Douglass AB, Boutros NN: The status of sleep abnormalities as a diagnostic test for major depressive disorder. *J Affect Disord* 2014; 156: 36–45.
55. Wilson S, Argyropoulos S: Antidepressants and sleep: a qualitative review of the literature. *Drugs* 2005; 65: 927–947.
56. Tribl GG, Wetter TC, Schredl M: Dreaming under antidepressants: a systematic review on evidence in depressive patients and healthy volunteers. *Sleep Med Rev* 2013; 17: 133–142.
57. Goodyer I, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ* 2007;335:142.
58. Pozzi M, Radice S, Clementi E, Molteni M, Nobile M: Antidepressants and, suicide and self-injury: causal or casual association? *Int J Psychiatry Clin Pract* 2016; 20: 47–51.
59. Leon AC, Fiedorowicz JG, Solomon DA, Li C, Coryell WH, Endicott J, Fawcett J, Keller MB: Risk of suicidal behavior with antidepressants in bipolar and unipolar disorders. *J Clin Psychiatry* 2014; 75: 720–727.
60. Baldessarini RJ, Tondo L, Strombom IM, Dominguez S, Fawcett J, Licinio J, Oquendo MA, Tollefson GD, Valuck RJ, Tohen M: Ecological studies of antidepressant treatment and suicidal risks. *Harv Rev Psychiatry* 2007; 15: 133–145.
61. Stone MB: The FDA warning on antidepressants and suicidality – why the controversy? *N Engl J Med* 2014; 371: 1668–1671.

62. Wilson E, Lader M: A review of the management of antidepressant discontinuation symptoms. *Ther Adv Psychopharmacol* 2015; 5: 357–368.
63. Fava GA, Gatti A, Belaise C, Guidi J, Offidani E: Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom* 2015; 84: 72–81.
64. Starcevic V, Brakoulias V, Viswasam K, Berle D: Inconsistent portrayal of medication dependence, withdrawal and discontinuation symptoms in treatment guidelines for anxiety disorders. *Psychother Psychosom* 2015; 84: 379–380.
65. Preskorn SH: Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 1995; 56(suppl 6):12–21.
66. Trindade E, Menon D, Topfer LA, Coloma C: Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *CMAJ* 1998; 159: 1245–1252.
67. Costagliola C, Parmeggiani F, Sebastiani A: SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs* 2004; 18: 475–484.
68. Trenque T, Herlem E, Auriche P, Drame M: Serotonin reuptake inhibitors and hyperprolactinaemia: a case/non-case study in the French pharmacovigilance database. *Drug Saf* 2011; 34: 1161–1166.
69. Ajmal A, Joffe H, Nachtigall LB: Psychotropic-induced hyperprolactinemia: a clinical review. *Psychosomatics* 2014; 55: 29–36.
70. Mondal S, Saha I, Das S, Ganguly A, Das D, Tripathi SK: A new logical insight and putative mechanism behind fluoxetine-induced amenorrhea, hyperprolactinemia and galactorrhoea in a case series. *Ther Adv Psychopharmacol* 2013; 3: 322–334.
71. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR: Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol* 2004; 103: 698–709.
72. Grigoriadis S, VonderPorten EH, Mamisashvili L, Tomlinson G, Dennis C-L, Koren G, Steiner M, Mousmanis P, Cheung A, Radford K, Martinovic J, Ross LE: The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. *J Clin Psychiatry* 2013; 74:e321–e341.
73. Larsen ER, Damkier P, Pedersen LH, Fenger-Gron J, Mikkelsen RL, Nielsen RE, Linde VJ, Knudsen HED, Skaarup L, Videbech P: Use of psychotropic drugs during pregnancy and breast-feeding. *Acta Psychiatr Scand* 2015; 132: 1–28.
74. Reis M, Källén B: Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects: a register study. *BMJ Open* 2013; 3:e002166.
75. Grigoriadis S, VonderPorten EH, Mamisashvili L, Rorecke M, Rehm J, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Ross LE: Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. *J Clin Psychiatry* 2013; 74:e293–e308.
76. Palmsten K, Hernández-Díaz S, Huybrechts KF, Williams PL, Michels KB, Achtyes ED, Mogun H, Setoguchi S: Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ* 2013; 347:f4877.
77. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA; Study NBDP: Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. *BMJ* 2015; 351:h3190.
78. Grigoriadis S, Vonderporten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Ross LE: Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and metaanalysis. *BMJ* 2014; 348:f6932.
79. Fava GA, Tomba E, Tossani E: Innovative trends in the design of therapeutic trials in psychopharmacology and psychotherapy. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 40: 306–311.
80. Fava G, Cosci F, Tomba E: Iatrogenic comorbidity in mental health. *Psychother Psychosom* 2015; 84(suppl 1):22.
81. Kaymaz N, van Os J, Loonen AJ, Nolen WA: Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 2008; 69: 1423–1436.