Mental Health, Psychiatric Drugs and Metabolism

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Mental health disorders are predominantly treated with psychiatric medications, which are licensed psychoactive drugs. This document focuses primarily on psychiatric drug induced mood changing side effects in relation to metabolisation. Metabolism is defined as an ability of the body to break down medications. Individual inability to break down medications efficiently causes toxicity resulting in side effects. This enlightening information falls outside the remit of mental health mainstream literature. Although 'side effects' is common terminology, Adverse Drug Reactions (ADRs) is the more accurate term as it reflects drug induced toxicities and is referred to throughout this document. The term antipsychotic is definitively replaced by neuroleptic, which means literally to 'seize the nerve'.[1]

Psychiatric Medications Adverse Drug Reactions

Many individuals treated with psychiatric medications experience severe ADRs, without any effective drug response.[2] Whilst antidepressant and neuroleptic drugs can cause iatrogenic physical ADRs, it is not widely known that psychiatric medications can induce mood changing behavioural ADRs. SSRIs for depression can precipitate deepening depression,[3] suicidal ideation,[4] suicide,[5] homicidal ideation,[6] homicide, akathisia and agitation,[7] mania and delirium,[8] severe anxiety, bizarre thinking and reasoning[9] psychosis,[10] and hallucinations.[11] Neuroleptics, used to treat psychosis, are linked with violence,[12] suicidal and homicidal behaviour[13] leading to completed suicide[14] and homicide.[15] These behavioural ADRs are toxic psychiatric disturbances.

So why do some individuals respond well to drugs and others not?

A major factor for varied drug responses is due to individuals' differing genetic makeup,[16] known as pharmacogenetics or drug metabolism. Although there are many metabolising systems in the body, the major metabolising systems for psychiatric medications are the CYP450 enzyme system, principally in the liver, and the serotonergic system. Both systems have an important role in the outcome of treatment, ADRs and efficacy.

Genotype Testing

CYP450, 5HTT-LPR and 5-HT receptor genotype testing can determine individual status for metabolizing psychiatric medications. Prescribers do not currently conduct genotype testing prior to treatment and take no account of whether or not individuals are able to efficiently metabolise medication.

Genotype testing of an individual prior to psychiatric medication treatment would enable assessment and prediction of potential neurotoxic behavioural ADRs in line with genotype status as depicted in the table above. The genotype test is a simple blood or swab test and in 2013 the standard cost of a test was £30. Retrospective genotyping for psychiatric drugs has demonstrated that there would have been a significant reduction in the financial outlay/cost based on the use of inappropriate medication and subsequent unnecessary healthcare costs.[17]

Genotype testing is used by pharmaceutical companies during medication trials (stages II - 1V), to de-select individuals who are PMs and liable to suffer severe ADRs. This practice includes trials with psychiatric medication to show medication in its best light.

References:

1. Principles of Psychopharmacology for Mental Health Professionals
By Jeffrey E. Kelsey, Charles B. Nemeroff, D. Jeffrey Newport.
2006, John Wiley & Sons.
Principles of Psychopharmacology for Mental Health ...

2. Bray J., Clarke C., Brennan G., Muncey T. Brennan G., Muncey T. (2008) Should we pushing meds'? The implication of pharmacogenomics. Journal of Psychiatric and Mental Health Nursing Vol.15 No.5 p.357-364
http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.516.227&rep=rep1&type=pdf

3. Medication Guide PAXIL® (paroxetine hydrochloride) Tablets & Oral Suspension. 2012, GlaxoSmithKline.
http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088676.pdf

4. Hansen L. Fluoxetine dose-increment related akathisia in depression: implications for clinical care, recognition and management of selective serotonin reuptake inhibitor-induced akathisia. J Psychopharmacol. 2003 Dec; 17(4):451-2.
http://www.ncbi.nlm.nih.gov/pubmed/14870959

5. Piatkov, I., Jones, T., & Van Vuuren, R. J. (2011). Suicide cases and venlafaxine. *Acta Neuropsychiatrica*, *23*(4), 156-160.
http://onlinelibrary.wiley.com/doi/10.1111/j.1601-5215.2011.00566.x/abstract

6. Medication Guide Effexor XR (venlafaxine hydrochloride) Extended-Release Capsules. Wyeth Pharmaceuticals Inc. Revised June 2013. Page 42, Nervous System
http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&ved=0CC4QFjAA&url=http%3A%2F%2Flabeling.pfizer.com%2Fshowlabeling.aspx%3Fid%3D100&ei=TPx0Usi_FNGRhQfCmYCQBA&usg=AFQjCNF_s-8vVVZ-mEjJthcCjADBhgLFiw&bvm=bv.55819444,d.ZG4

7. Lucire Y, Crotty C. Antidepressant-induced akathisia-related homicides associated with diminishing mutations in metabolizing genes of the CYP450 family. Pharmacogenomics and Personalized Medicine. 2011;4:65-81. doi:10.2147/PGPM.S17445
http://www.dovepress.com/getfile.php?fileID=10671

8. Patient information leaflet and Summary of Product Characteristics for Venlafaxine, electronic Medicines Compendium, eMC.
http://www.medicines.org.uk/emc/default.aspx accessed 6th Sept. 2013

9. Fouks, Perivier, Mathis et al. Le Syndrome d' impatience. Ann Medico-psychol 138: pp719-723 (1968)
Source: Van Putten T. The many faces of akathisia. Compr Psychiatry. 1975 Jan-Feb; 16(1): 43-7. doi:10.1016/0010-440X(75)90019-X
http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/VanPuttenManyFacesofAkathisia.PDF

10. What Did Eli Lilly Know About Prozac Induced Violence & Suicidality?
Baum Hedlund, law firm, reproduces the time-line presented to the jury in the Forsyth v. Eli Lilly Trial during closing arguments by the plaintiffs.
http://ahrp.org/what-did-eli-lilly-know-about-prozac-induced-violence-suicidality/

11. Food and Drug Administration, FDA medication Guide, Paxil, GlaxoSmithKline
http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088676.pdf
accessed 25th March 2014

12. Herrera JN, Sramek JJ, Costa JF, Swati R, Heh C, Nguyen BN. High Potency Neuroleptics and Violence in Schizophrenics. Journal of Nervous & Mental Disease.1988 Sept; 176 (9):519-580. doi:10.1097/00005053-198809000-00009
http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/HerreraNeurolepticsandViolence.PDF

13. Van Putten, T., & Marder, S. R. Behavioral toxicity of antipsychotic drugs. Journal of Clinical Psychiatry. 1987, vol. 48, suppl., pp. 13-19
http://psycnet.apa.org/psycinfo/1988-30523-001

14. Healy, D., Harris, M., Tranter, R., Gutting, P., Austin, R., Jones-Edwards, G., & Roberts, A. P. (2006). Lifetime suicide rates in treated schizophrenia: 1875–1924 and 1994–1998 cohorts compared. The British Journal of Psychiatry, 188(3), 223-228.
http://bjp.rcpsych.org/content/188/3/223.full

15. Schulte JL. HOMICIDE AND SUICIDE ASSOCIATED WITH AKATHISIA AND HALOPERIDOL. American Journal of Forensic Psychiatry. 1985;6:3-7.
http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/Schulte.PDF

16. Kirk M., Tonkin E., Skirton H., et al. Genetics in mental health nursing: is it part of your role? Mental Health Practice (2006) 10, 15–18.

17. Winner J, Allen JD, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Translational Psychiatry. 2013 Mar 19;3:e242. doi:10.1038/tp.2013.2
http://www.nature.com/tp/journal/v3/n3/full/tp20132a.html

APPENDIX

450CYP Enzyme System

75% of psychiatric[18] including antidepressant and neuroleptic medications are metabolised through CYP2D6, which is one of the most variable metabolizing enzyme pathways known. Other pathways that metabolise antidepressants and neuroleptic drugs include CYPC19, CYPC9, CYP1A2, CYP 3A4 and CYPA5.

Genetic variations, known as alleles, classify individuals as either being Poor Metaboliser (PM), Intermediate Metaboliser (IM), Extensive Metaboliser (EM) or Ultra Metaboliser (UM) genotypes.[19] PMs have two non-functional alleles and IMs have one non-functional allele plus one diminished allele or two diminished alleles or two partially active alleles.[20] UMs have more than two active gene copies on the same allele, or increased expression of a single allele.[7] EMs have one or at the most two functional alleles with 'normal 'activity.[20]

Genetic variability affects psychiatric medication outcomes. PMs and IMs incur neurotoxicities leading to violent acts, as do UMs with prodrug use. EM individuals are likely to have a therapeutic response without neurotoxic ADRs.

EMs determine the window of opportunity for a drug therapeutic level and sets the recommended drug dosage. This is important, as drug companies do not specify drug dosage for UMs, IMs and PMs, which explains why these individuals do not respond well to standard drug doses.

Table 1. General Population Frequency of CYP450 Genotypes:

Gene	PM	IM	PM & IM	EM	UM
CYP 2D6	10%	35%	45%	48%	7%
CYP 2C19	3-21%	24-36%	27% - 57%	~60%	N/A
CYP 2C9	4%	38%	42%	14-44%	30%

Ref 21

Table 2. Population Frequency for Poor Metabolisers of CYP450 2D6, 2C19 and 2C9 Pathways

2D6 PM	2C19 PM	2C9 PM
5 - 10% of Caucasians[22]	2-6% of Caucasians[23]	35% of Caucasians[24]
41% Pacific Islanders[22]	41% Asians[22]	42% Croatians [25]
6.3% Africans[26]	10-20% Africans[27]	0.5-4% Africans & Asian [28]
14.5%African American [26]	Up to 90% Melanesians [29]	
	15-20% Japanese [27]	

Combined PM and IM frequency via CYP450 2D6:[30]

26% Caucasians
40-50% African-Americans
50% Africans[30]

Statistically, **Black Minority and Ethnic (BME) populations** have greater difficulty metabolising psychiatric medications compared with White and Asian population, due to the higher frequency of lower metabolism at CYP 2D6.[31] BME groups are four times more likely to experience psychosis than Caucasians,[32] with *African* Caribbean people three to five times more likely than any other group, of being diagnosed with schizophrenia and admitted to hospital.[33]

Serotonergic

Antidepressants[33] and neuroleptics[34] are regulated through the serotonergic system. The serotonin system consists of the Serotonin Transporter Gene and serotonin receptors (5-HT). As with the CYP450 system, the serotonergic system has genetic variations that affect outcomes.

Serotonin Transporter Gene and Antidepressants

Genetic variations in the promoter region of the Serotonin Transporter Gene (5HTT-LPR) are coded as L/L (2 long alleles), L/S (a long and a short allele) or S/S (2 short alleles). Those individuals with the L/L code have a 'normal' gene activity and respond well to antidepressant medications.[36] In contrast individuals with the short allele have slower gene activity, resulting in a reduction of serotonin transmission. Both L/S and S/S individuals treated with antidepressants have poor outcomes,[37] and a 'powerfully predicted non response'.[38] Emerging antidepressant ADRs[39] are inevitable for individuals with the short allele.

Individual response to neuroleptic medication is also affected by 5HTT-LPR variations. 50% of individuals coded L/L receiving neuroleptic treatment with haloperidol experienced parkinsonian side effects; however the incidence of parkinsonian side effects for L/S and S/S allele individuals rose to 62.2% and 83.1% respectively.[40]

What is the population frequency of 5HTT-LPR gene variants?

Individuals coded with (S/S) and (S/L) genotype:

Caucasians S/S (39%)[41 Heils]
Caucasians S/L (52%)[41 Heils]
East Asians S/S (49–74%)[42 Goldman]
Native Americans S/S (42%)[42 Goldman]
African Americans S/S (7–17%)[42 Goldman]

Individuals coded with L/L genotype:

Caucasians (29–43%)[42]
African Americans (45–56%)[42]
Native American (10–14%)[42]
East Asian samples (1–13%)[42]

Serotonin Receptors

There are 14 types of 5-HT receptors that can be targeted by antidepressants and neuroleptics.[43] However the 5-HT 2A serotonin receptor variant, in particular, is associated with individual poor response and increased risk of ADRs when treated with antidepressant selective serotonin reuptake inhibitors.[44] This same receptor variant has been linked to poor response from some individuals having neuroleptic treatment.[45]

Table 3. The Link between Genotype Status and Psychiatric Disturbances for CYP450, 5HTT-LPR and 5-HT Allele Variants when treated with Antidepressant Medications

NEUROTOXIC BEHAVIOURAL ADRs	CYP450 AND SEROTONERGIC GENETIC VARIANTS
Akathisia/agitation/ restlessness	CYP450 2D6 and 2C19 non-functional alleles[7] CYP450 2D6 and 2C9 diminished function alleles[7] CYP450 2C19 ultra rapid multiple allele duplications[7] CYP2C9 non-functional alleles [46] 5-HTT-LPR short allele [47, 48] 5-HTR2A receptor variant[44]
Suicide/suicide risk	CYP450 2D6, 2C19 and 2C9 non-functional and diminished function alleles.[7, 46] CYP450 2D6 ultra rapid multiple allele duplications[7] 5-HT1AC receptor variant[49]
Homicide/attempted homicide	CYP450 2D6 and 2C19 non-functional[7] CYP450 2D6 and 2C9 diminished function alleles[7] CYP450 2C19 ultra rapid multiple allele duplications[7]
Insomnia	5-HTTLPR short allele[47]
Mania /delirium	CYP450 2D6 and 2C19 non-functional alleles[7] CYP450 2D6 and 2C9 diminished function alleles[7] CYP450 2C19 ultra rapid multiple allele duplications[7] 5-HTTLPR short allele [48, 50]
Serotonin Syndrome	CYP450 2D6 IM[51]
Psychosis	CYP2D6 non- functional and diminished allele[46]
Delusions	CYP2D6 diminished allele[46]
Dysphoria	CYP2D6 non-functional allele and diminished function allele[46]
Hallucinations	CYP2D6 non-functional allele and diminished function allele[46]

Antidepressants linked with Psychiatric Disturbances and Genetic Variations

Fluoxetine
Paroxetine
Sertraline
Escitalopram
Citalopram
Venlafaxine

Discussion

Neurotoxic behavioural ADRs are not understood in psychiatry. When individuals do not respond therapeutically to psychiatric medication or show neuropsychiatric disturbances, the practice in mental heath is to increase the dose and/or polypharmacy. This practice is futile as further medications increase neurotoxicities. Individuals are theoretically being overdosed, albeit unwittingly by prescribers. Prescribing of psychiatric medications is done on a trial end error basis. Individual suffering is immense. This needs to change.

References

18. Arehart-Treichel J. Gene Testing Could Help Predict Drug Responses. Psychiatric News. May 20, 2005 Volume 40 Number 10 p.33.Clinical & Research News.
http://psychnews.psychiatryonline.org/newsarticle.aspx?articleid=108990

19. Bondy B. & Spellmann I. (2007) Pharmacogenetics of antipsychotics: useful for the clinician? *Current Opinion in Psychiatry* 20, 126–130.
Source: Bray J., Clarke C., Brennan G., Muncey T. (2008) Should we pushing meds'? The_implication of pharmacogenomics. Journal of Psychiatric and Mental Health Nursing Vol.15 No.5 p.357-364 http://www.psychological-wellbeing.co.uk/?download=Should_we_be_pushing_meds.pdf

20. Pilgrim, J. L., Dimitri Gerostamoulos, and Olaf H. Drummer. "Review: Pharmacogenetic aspects of the effect of cytochrome P450 polymorphisms on serotonergic drug metabolism, response, interactions, and adverse effects." *Forensic science, medicine, and pathology* 7.2 (2011): 162-184.

21. Population Frequency of Cytochrome P450 (CYP450) genotypes. Accessed 21st June 2013
http://youscript.com/healthcare-professionals/what-is-youscript/pharmacogenetic-testing/

22. J de Leon, Armstrong SC, Cozza KL. Clinical Guidelines for Psychiatrists for the Use of Pharmacogenetic Testing for CYP450 2D6 and CYP450 2C19. Med-Psych Drug-Drug Interactions Update. Psychosomatics 47:1, January-February 2006
http://cellulargenetix.com/pdfs/2006_PGX_Clinical_Guidelines.pdf

23. Kaneko A, Lum JK, Yaviong L, Takahashi N, Ishizaki T, Bertilsson L, Kobayakawa T, Björkman A. High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. Pharmacogenetics. 1999 Oct;9(5):581-90. PubMed PMID: 10591538.
http://www.ncbi.nlm.nih.gov/pubmed/10591538

24. Lee CR, Goldstein JA, Pieper JA. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenetics. 2002 Apr;12(3):251-63. Review. Erratum in: Pharmacogenetics 2002 Jun;12(4):343.
http://www.ncbi.nlm.nih.gov/pubmed/11927841

24 Geneticks Istanbul. CYP2C9 Clinical significance
http://www.prosignaturkiye.com/tr/cyp2c9

26. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics. 2002 Mar; 3(2):229-43. http://www.ncbi.nlm.nih.gov/pubmed/11972444

27. Cytochrome CYP450 2C19 Genotyping YouScript™ Accessed 14th Feb 2013 http://youscript.com/healthcare-professionals/what-is-youscript/pharmacogenetic-testing/cytochrome-p450-2c19-genotyping/

28. Cytochrome P450 2C9 Genotyping YouScript™ Accessed 14th Feb 2013 http://youscript.com/healthcare-professionals/what-is-youscript/pharmacogenetic-testing/cytochrome-p450-2c9-with-vkor-for-warfarin/

29. Sistonen, J. Pharmacogenetic Variation at CYP2D6, CYP2C9, and CYP2C19: Population Genetic and Forensic Aspects. Department of Forensic Medicine University of Helsinki Finland. (2008) Page 22. http://doria17-kk.lib.helsinki.fi/bitstream/handle/10024/42557/pharmaco.pdf?sequence=2

30. Cytochrome CYP2D6 Genotyping Genelex. Accessed 21st June 2013 http://genelex.com/pharmacogenetic-tests/cyp2d6/

31. Andrea Gaedigk, MS, PhD, L. DiAnne Bradford, PhD, Kenda A. Marcucci, BS, and J. Steven Leeder, PharmD, PhD. (2002). Unique CYP2D6 activity distribution and genotype-phenotype discordance in black Americans. Clinical Pharmacology & Therapeutics, 72, 76-89. http://www.nature.com/clpt/journal/v72/n1/absc/clpt200267a.html

32. Mental Health Equalities. National Mental Health Development Unit. (NMHDU) BME Groups and Mental Health – Presentation and Evidence to the Centre for Social Justice Mental Health Review 18 October 2010. www.nmhdu.org.uk/silo/files/bme-groups-and-mental-health-.doc accessed 7th Sept. 2013

33. Mental Health Foundation - Black and Minority Ethnic Communities http://www.mentalhealth.org.uk/help-information/mental-health-a-z/B/BM ok E-communities/ accessed 7th Sept. 2013

34. Charles H. Brown, MS Pharm, RPh, CACP. Drug-induced Serotonin Syndrome, Causative agents. Medscape, News and Perspective. US Pharmacist © 2010 Jobson Publishing.

35. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology. 1999 Aug;21(2 Suppl):106S-115S. Review. PubMed http://www.ncbi.nlm.nih.gov/pubmed/10432496

36. Pollock, Bruce G., et al. "Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression." *Neuropsychopharmacology* 23.5 (2000): 587-590. http://www.nature.com/npp/journal/v23/n5/full/1395540a.html#bib7

37. Murphy, G. M., Hollander, S. B., Rodrigues, H. E., Kremer, C., & Schatzberg, A. F. (2004). Effects of the Serotonin Transporter Gene Promoter Polymorphism on Mirtazapine and Paroxetine Efficacy and Adverse Events in Geriatric Major Depression. *Archives of general psychiatry*, *61*(11), 1163-1169. http://archpsyc.jamanetwork.com/article.aspx?articleid=482088

38. Kim, D. K., Lim, S. W., Lee, S., Sohn, S. E., Kim, S., Hahn, C. G., & Carroll, B. J. (2000). Serotonin transporter gene polymorphism and antidepressant response. Neuroreport, 11(1), 215-219. http://journals.lww.com/neuroreport/Abstract/2000/01170/Serotonin_transporter_gene_polymorphism_and.42.aspx

39. Karlović D, Karlović D. "Serotonin Transporter Gene (5-HTTLPR) Polymorphism and Efficacy of Selective Serotonin Reuptake Inhibitors–Do We Have Sufficient Evidence for Clinical Practice." Acta Clin Croat. 2013 Sep;52(3):353-62. Review. http://www.ncbi.nlm.nih.gov/pubmed/24558768

40. Han, D., et al. "The association between tardive dyskinesia induced by haloperidol and polymorphisms in the serotonin transporter gene and catecholamine-O-methyltransferase gene in Korean schizophrenic patients." *Clinical Psychopharmacology and Neuroscience* 3.1 (2005): 16. http://pdf.medrang.co.kr/Cpn/2005/003/Cpn003-01-03.pdf

41. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP. (1996): Allelic variation of human serotonin transporter gene expression. J Neurochemistry 66: 2621–2624

42. Goldman N, Glei DA, Lin Y-H, Weinstein M. The Serotonin Transporter Polymorphism (5-HTTLPR): Allelic Variation and Links with Depressive Symptoms. *Depression and anxiety*. 2010;27(3):260-269. doi:10.1002/da.20660. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841212/

43. Jackson GE. *Rethinking Psychiatric Drugs: A Guide for Informed Consent.* Page 220. Bloomington, IN: Author House. 2005.

44. Murphy GM Jr, Kremer C, Rodrigues HE, et al: Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160(10):1830-1835 http://ils.unc.edu/bmh/neoref/this.dir.unneeded/schizophrenia/review/tmp/510.pdf

45. Zhang, Jian-Ping, and Anil K. Malhotra. "Pharmacogenetics and Antipsychotics: Therapeutic Efficacy and Side Effects Prediction." *Expert opinion on drug metabolism & toxicology* 7.1 (2011): 9–37. *PMC*. Web. 12 Sept. 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057913/

46. Piatkov, Irina, Trudi Jones, and Mark McLean. "Cases of Adverse Reaction to Psychotropic Drugs and Possible Association with Pharmacogenetics." *Journal of personalized medicine* 2.4 (2012): 149-157. http://www.mdpi.com/2075-4426/2/4/149/htm

47. Perlis RH, Mischoulon D, Smoller JW, Yu-Jui Yvonne Wan, Lamon-Fava S, Keh-Ming Lin, et al. Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. Biological Psychiatry – 1 November 2003 (Vol. 54, Issue 9, Pages 879-883. http://www.sciencedirect.com/science/article/pii/S0006322303004244

48. Spinelli et al. 2007
Source: Renaud Jardri, Arnaud Cachia, Pierre Thomas, Delphine Pins "The Neuroscience of Hallucinations" Page 240. ISBN 978-1-46i4-4120-5. Springer, New York, 2013. The Neuroscience of Hallucinations - Page 240 - Google Books

49. Sawiniec J, Borkowski K, Ginalska G, Lewandowska-Stanek H. Association between 5-hydroxytryptamine 1A receptor gene polymorphism and suicidal behavior. Przegl Lek. 2007;64(4-5):208-11. PubMed PMID: 17724868. http://www.ncbi.nlm.nih.gov/pubmed/17724868

50. Mundo E, Walker M, Cate T, Macciardi F, Kennedy JL. The Role of Serotonin Transporter Protein Gene in Antidepressant-Induced Mania in Bipolar Disorder: Preliminary Findings. *Arch Gen Psychiatry*. 2001;58(6):539-544. http://archpsyc.jamanetwork.com/article.aspx?articleid=481790

51. Sato A, Okura Y, Minagawa S, Ohno Y, Fujita S, Kondo D, Hayashi M, Komura S, Kato K, Hanawa H, Kodama M, Aizawa Y. Life-threatening serotonin syndrome in a patient with chronic heart failure and CYP2D6*1/*5. Mayo Clin Proc. 2004 Nov;79(11):1444-8. http://www.ncbi.nlm.nih.gov/pubmed/15544025