Human Biomarkers of Rapid Antidepressant Effects

Supplemental Information

Table S1. Common biomarker tools used in treatment trials for mood disorders

Biomarker tools used to study MDD	Recent reviews discussing approach and findings
Positron emission tomography (PET)	Mayberg *et al.* 2003; Takano *et al.* 2010 (1, 2)
Single photon emission computerized tomography (SPECT)	Huang *et al.* 2010; Rigucci *et al.* 2010 (3, 4)
Functional magnetic resonance imaging (fMRI)	Delvecchio *et al.* 2012 (5)
Brain proton magnetic resonance spectroscopy (1H-MRS)	Caverzasi *et al.* 2012 (6)
Neurophysiological measures (e.g. sleep EEG, MEG, LDAEP)	Pillai *et al.* 2011; Leiser *et al.* 2011; Williams *et al.* 2010; Hegerl & Juckel 2000; Hegerl *et al.* 2001 (7-11)
Peripheral blood, plasma, and urine markers (e.g. cortisol, BDNF, VEGF)	Schmidt *et al.* 2011; Tadic *et al.* 2011 (12, 13)
Cerebrospinal fluid (CSF)	Ditzen *et al.* 2012; Raedler & Wiedemann 2006 (14, 15)
Saccadic eye movements (marker of serotonergic subtype 5-HT2A activity in brainstem)	Flechtner *et al.* 1997 (16)
Genetics	Weizman *et al.* 2012 (17)
Proteomics	Kobeissy *et al.* 2008; Filiou *et al.* 2011 (18, 19)
Metabolomics	Quinones & Kaddurah-Daouk 2009 (20)

BDNF, brain-derived neurotrophic factor; EEG, electroencephalogram; LDAEP, loudness dependence auditory evoked potentials; MEG, magnetoencephalography; VEGF, vascular endothelial growth factor.

Table S2. Limitations of developing biomarkers with conventional antidepressant treatments

Factors	**Conventional antidepressants (i.e., lag of onset of antidepressant action)**	**Rapid acting interventions**
Sample size/Recruitment	Larger number of subjects needed	Fewer number of subjects needed
Overall attrition	Higher given length of trials	Lower
Cost	Significantly higher given clinical costs	Lower
Adherence to protocol	More difficult to monitor; more susceptible to influence of alcohol or illicit drug use	Much improved; compliance ensured with use of intravenous study drugs
Speed of developing biomarkers of response	Prolonged time in developing biomarkers of response, because trials are usually lengthy 8-12 weeks (for acute phase)	Much more rapid; could rapidly lead to testing of many compounds within a relatively short period of time
Personalizing treatment	Would apply to personalizing treatment with current antidepressants	May not apply to personalizing treatment, especially to current antidepressants

Supplemental References

1. Mayberg HS (2003): Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clin N Am* 13:805-815.
2. Takano A (2010): The application of PET technique for the development and evaluation of novel antipsychotics. *Curr Pharm Des* 16:371-377.
3. Huang Y, Zheng MQ, Gerdes JM (2010): Development of effective PET and SPECT imaging agents for the serotonin transporter: has a twenty-year journey reached its destination? *Curr Top Med Chem* 10:1499-1526.
4. Rigucci S, Serafini G, Pompili M, Kotzalidis GD, Tatarelli R (2010): Anatomical and functional correlates in major depressive disorder: the contribution of neuroimaging studies. *World J Biol Psychiatry* 11:165-180.
5. Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, *et al.* (2012): Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. *Eur Neuropsychopharmacol* 22:100-113.
6. Caverzasi E, Pichiecchio A, Poloni GU, Calligaro A, Pasin M, Palesi F, *et al.* (2012): Magnetic resonance spectroscopy in the evaluation of treatment efficacy in unipolar major depressive disorder: a review of the literature. *Funct Neurol* 27:13-22.
7. Pillai V, Kalmbach DA, Ciesla JA (2011): A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. *Biol Psychiatry* 70:912-919.
8. Leiser SC, Dunlop J, Bowlby MR, Devilbiss DM (2011): Aligning strategies for using EEG as a surrogate biomarker: a review of preclinical and clinical research. *Biochem Pharmacol* 81:1408-1421.
9. Williams MA, Sachdev PS (2010): Magnetoencephalography in neuropsychiatry: ready for application? *Curr Opin Psychiatry* 23:273-277.
10. Hegerl U, Juckel G (2000): Identifying psychiatric patients with serotonergic dysfunctions by event-related potentials. *World J Biol Psychiatry* 1:112-118.
11. Hegerl U, Gallinat J, Juckel G (2001): Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? *J Affect Disord* 62:93-100.
12. Schmidt HD, Shelton RC, Duman RS (2011): Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. *Neuropsychopharmacology* 36:2375-2394.
13. Tadic A, Wagner S, Gorbulev S, Dahmen N, Hiemke C, Braus DF, *et al.* (2011): Peripheral blood and neuropsychological markers for the onset of action of antidepressant drugs in patients with Major Depressive Disorder. *BMC Psychiatry* 11:16.
14. Ditzen C, Tang N, Jastorff AM, Teplytska L, Yassouridis A, Maccarrone G, *et al.* (2012): Cerebrospinal fluid biomarkers for major depression confirm relevance of associated pathophysiology. *Neuropsychopharmacology* 37:1013-1025
15. Raedler TJ, Wiedemann K (2006): CSF-studies in neuropsychiatric disorders. *Neuro Endocrinol Lett* 27:297-305.
16. Flechtner KM, Steinacher B, Sauer R, Mackert A (1997): Smooth pursuit eye movements in schizophrenia and affective disorder. *Psychol Med* 27:1411-1419.
17. Weizman S, Gonda X, Dome P, Faludi G (2012): Pharmacogenetics of antidepressive drugs: a way towards personalized treatment of major depressive disorder. *Neuropsychopharmacol Hung* 14:87-101.

18. Kobeissy FH, Sadasivan S, Liu J, Gold MS, Wang KK (2008): Psychiatric research: psychoproteomics, degradomics and systems biology. *Expert Rev Proteomics* 5:293-314.
19. Filiou MD, Turck CW, Martins-de-Souza D (2011): Quantitative proteomics for investigating psychiatric disorders. *Proteomics Clin Appl* 5:38-49.
20. Quinones MP, Kaddurah-Daouk R (2009): Metabolomics tools for identifying biomarkers for neuropsychiatric diseases. *Neurobiol Dis* 35:165-176.