Polypharmacy in oligopopulations: what psychiatric genetics can teach biological psychiatry

Alexander B. Niculescu III

Psychiatric genetics and genomics have made major strides in recent years. Some of that knowledge has yet to permeate in the clinical practice of biological psychiatry. The example of cancer-genetics, biology and clinical treatments may be profitable in terms of accelerating translational integration in psychiatry. We propose that current developments in genetics and genomics point to an Early Low-Dose Rational Polypharmacy in Oligopopulations model for psychiatric pharmacotherapy. *Psychiatr Genet* 16:241–244 © 2006 Lippincott Williams & Wilkins.

Psychiatric Genetics 2006, **16**:241–244

Keywords: biological psychiatry, genetics, personalized medicine, polypharmacy

Laboratory of Neurophenomics, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence and requests for reprints to Alexander B. Niculescu III, MD, PhD, Laboratory of Neurophenomics, Institute of Psychiatric Research, Indiana University School of Medicine, 791 Union Drive, Indianapolis, IN 46202, USA
E-mail: anicules@iupui.edu

Point of View Section: Genetics in Neuroscience

We are starting a new Point of View Section called ''Genetics in Neuroscience''. It will be focused on how psychiatric genetics and genomics inform, and are in turn informed by, the broader body of work in neurosciences. Our premise is that advances in different fields can bootstrap and reinforce each other in a Bayesian fashion, leading to breakthroughs that each field alone may not have been able to make. While craftsmanship is to be prized at all times in any scientific field, and it is particularly appreciated in mature fields like psychiatric genetics, creativity has its place in moving fields forward, sometimes dramatically. We hope this section will be a forum for new ideas and perspectives that will spur on discussions and, more importantly, future interdisciplinary collaborative work.

John I. Nurnberger, Jr, MD, PhD, Editor

Alexander B. Niculescu, III, MD, PhD, Assistant Editor, Point of View Section Editor.

Future submissions for this section should be addressed to the attention of Dr Niculescu (anicules@iupui.edu)

Accepted 25 August 2006

The genetic and genomic landscape

On the basis of the accumulated evidence so far, most psychiatric disorders are thought to be complex, polygenic, non-Mendelian, with variable penetrance, and with small effect genes acting in epistasis, in different combinations and permutations, in different subpopulations (Nurnberger, 2002; Ogden *et al.*, 2004; Preston and Weinberger, 2005). Moreover, the developmental history of each individual has likely sculpted their gene expression landscape through gene–environment interactions (Anthony, 2001; Abdolmaleky *et al.*, 2004). This is the terrain on which our medications must act to correct imbalances.

Early

As in the field of cancer therapy, early intervention may be key in terms of preventing the full-blown accumulation of neurobiological abnormalities associated with clinical illness. In other words, we should not let the illness 'metastasize'. We in psychiatry have much to learn, and should actively borrow from cancer research and treatment – methodologically and paradigmatically (Lu *et al.*, 2005; Pages *et al.*, 2005). Although our focus in psychiatry has been so far primarily on discovering disease causing genes, we should pay as much attention to disease-protecting genes and how we can enhance their functionality. That Yin-Yang duality is fully appreciated in the cancer field, as oncogenes and tumor-suppressor genes (Vogelstein and Kinzler, 2004). We had proposed earlier similar terms for genes involved in psychiatric disorders, psychogenes and psychosis-suppressor genes (Niculescu *et al.*, 2000). A debate on this is welcome, not least in terms of coming up with a more felicitous terminology, perhaps disease specific: schizogenes and schizophrenia-suppresing genes, bipologenes and bipolar-suppressing genes, anxiogenes and anxiety-suppressing genes.

Low dose

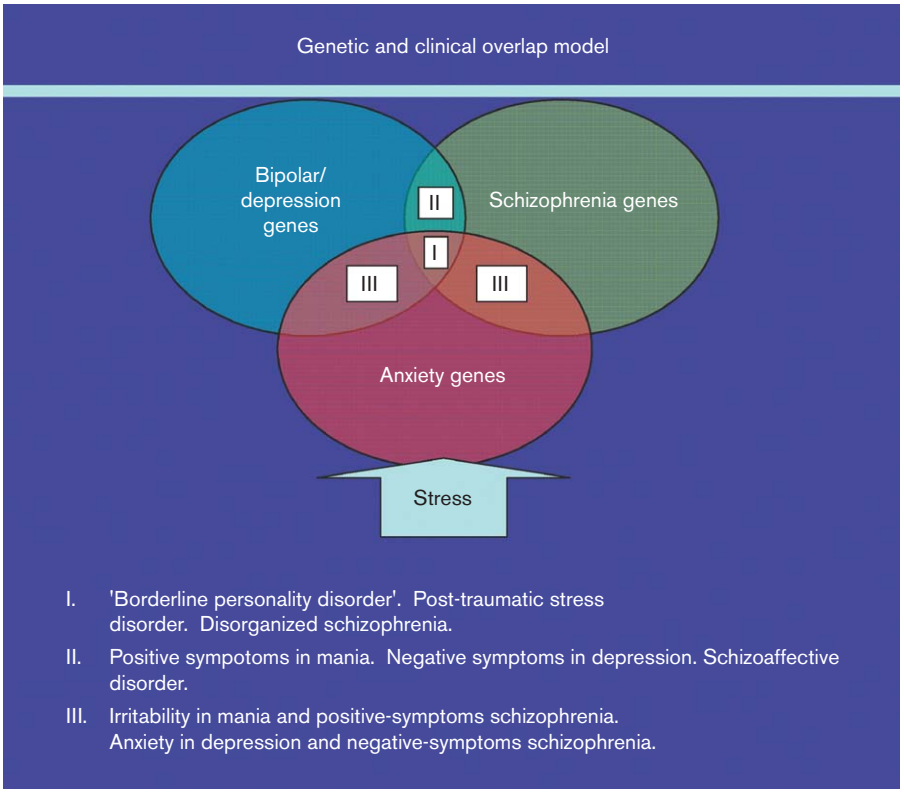
As most psychiatric genes seem to have small effects (Barrett *et al.*, 2003; Lasky-Su *et al.*, 2005), a likely reflection of the epistasis of the different genetic pathways involved at the same time, low-dose rather than high-dose polypharmacy may be all that is needed. In this way, one not only gets synergistic benefits, but also avoids side effects generally associated with higher doses (Volavka *et al.*, 2004).

Rational polypharmacy

Multiple genes and pathways involved mean that we have to use polypharmacy or 'dirty drugs'. A good example of the latter is clozapine, one of the most effective,

0955-8829

Fig. 1



Genetic and clinical overlap model.

broad-spectrum psychiatric drugs at our disposal (Tandon and Fleischhacker, 2005), which is also among the 'dirtiest' in terms of activity on multiple neurotransmitter receptors and pathways. Most complex and refractory psychiatric patients present with cognitive, mood and anxiety symptoms, and thus require all three dimensions to be addressed for complete and stable remission (Fig. 1). This can be accomplished through 'dirty drugs', such as atypical antipsychotics, or through three-dimensional polypharmacy. Polypharmacy gives us more flexibility in adjusting the dosages of the different activities, rather than the fixed ratios of the moieties in single molecules. This is already part of clinical practice, but done empirically, by default and often not rationally (Post *et al.*, 1996). We need to start using the genes and pathways identified by genetics and genomic research as a guide in our rational choice of medication combinations (Ogden *et al.*, 2004). To ensure patient compliance, which is an underappreciated cause of treatment failure, we cannot have the medication regimens too complex. Having multiple drugs in a single pill, with different dosage strengths, is a reasonable compromise strategy. An example of that in psychiatry is the olanzapine/fluoxetine combination. The trend is well advanced in other medical specialties, see for example the combination 'polypills' of antihypertensive or anti-HIV drugs.

Oligopopulations

Moreover, the issues of genetic and phenotypic heterogeneity of populations (Breslau *et al.*, 2005), of overlap and clinical comorbidity of disorders, and of interdependence of symptoms (Schuckit *et al.*, 1997; MacKinnon *et al.*, 2002; Berrettini, 2003; Lewinsohn *et al.*, 2004; Niculescu, 2004; Ogden *et al.*, 2004; Craddock *et al.*, 2005; Craddock and Owen 2005; Niculescu *et al.*, 2006) (Fig. 1) mean that, like in cancer, studies looking at the effect of a drug in large, nonenriched population samples may not pick up a strong signal for effects or for side effects, as was arguably the case for antipsychotics in the clinical antipsychotic trials of intervention effectiveness trial (Lieberman *et al.*, 2005). Identifying which small subpopulations (oligopopulations) best respond to a drug or a combination of drugs, and have the least side effects, is the key to speeding up drug development, improving efficacy and avoiding adverse events and re-calls (Niculescu and Akiskal, 2001; Prathikanti and Weinberger, 2005). One solution is phenotypic profiling

(phenomics) (Kelsoe and Niculescu, 2002; Freimer and Sabatti, 2003; Schulze and McMahon, 2004; Bearden and Freimer, 2006; Niculescu *et al.*, 2006) in conjunction with genetic and genomic profiling to be performed as part of all early clinical trials, and the results of the analysis of that data to be fed into the design of later trials with enriched populations of responders vs 'adverse-effectors'. Identifying biomarkers of psychiatric disorders whether from imaging studies (Pien *et al.*, 2005) or peripheral blood profiling (Glatt *et al.*, 2005; Tsuang *et al.*, 2005; Segman *et al.*, 2005), likely best accomplished by using multipronged Bayesian strategies such as convergent functional genomics (Niculescu *et al.*, 2000; Ogden *et al.*, 2004; Bertsch *et al.*, 2005) and integrative genomics (Garraway *et al.*, 2005), would be particularly useful for drug development, diagnosis and early intervention efforts. Ultimately, our field, like others, is moving in the direction of personalized medicine.

Gene × environment × drug interactions

As to the issue of individual patient history, temperament (Evans *et al.*, 2005; Cloninger *et al.*, 2006), gene–environment interactions (Moffitt *et al.*, 2005; Rutter *et al.*, 2006) and drug response, that may remain for a time part of the empirical trial and error aspect of day-to-day clinical practice. Epidemiological crunching of large data sets of patient history information, including demographics and medical comorbidities (macrophenomics), may asymptotically reduce uncertainty over time, and should be pursued vigorously. Pharmacogenomic research has started to prove its usefulness in psychiatry (Malhotra *et al.*, 2004; de Leon, 2006). Healthcare systems (such as the Veterans Administration Healthcare System in the US) and clinical trials in which all patient information is computerized are particularly amenable to the application of this database mining type of research. One could envisage the use of profiling algorithms similar to those used in the financial and insurance industries, ending up with a numerical score for each patient in relationship to a particular drug treatment combination. On the basis of that, the clinicians of the future could make a decision to proceed or not with that particular treatment.

Conclusions

Current treatment regimens in biological psychiatry follow a 'Oligopharmacy in polypopulations' model. We propose that psychiatric genetics and genomics point to a need for a 'Polypharmacy in oligopopulations' approach. Although that may seem onerous for the pharmaceutical drug development process, in the long run this targeted approach should lead to more Food and Drug Administration approvals (more efficient drugs) and less withdrawals from the market (less side effects). The ultimate beneficiaries are, of course, the patients, their families and society at large.

References

Abdolmaleky HM, Smith CL, Faraone SV, Shafa R, Stone W, Glatt SJ, Tsuang MT (2004). Methylomics in psychiatry: modulation of gene–environment interactions may be through DNA methylation. *Am J Med Genet B Neuropsychiatr Genet* **127**:51–59.

Anthony JC (2001). The promise of psychiatric enviromics. *Br J Psychiatry Suppl* **40**:s8–s11.

Barrett TB, Hauger RL, Kennedy JL, Sadovnick AD, Remick RA, Keck PE, *et al.* (2003). Evidence that a single nucleotide polymorphism in the promoter of the G protein receptor kinase 3 gene is associated with bipolar disorder. *Mol Psychiatry* **8**:546–557.

Bearden CE, Freimer NB (2006). Endophenotypes for psychiatric disorders: ready for primetime? *Trends Genet* **22**:306–313.

Berrettini W (2003). Evidence for shared susceptibility in bipolar disorder and schizophrenia. *Am J Med Genet C Semin Med Genet* **123**:59–64.

Bertsch B, Ogden CA, Sidhu K, Le-Niculescu H, Kuczenski R, Niculescu AB (2005). Convergent functional genomics: a Bayesian candidate gene identification approach for complex disorders. *Methods* **37**:274–279.

Breslau N, Reboussin BA, Anthony JC, Storr CL (2005). The structure of posttraumatic stress disorder: latent class analysis in 2 community samples. *Arch Gen Psychiatry* **62**:1343–1351.

Cloninger CR, Svrakic DM, Przybeck TR (2006). Can personality assessment predict future depression? A twelve-month follow-up of 631 subjects. *J Affect Disord* **92**:35–44.

Craddock N, Owen MJ (2005). The beginning of the end for the Kraepelinian dichotomy. *Br J Psychiatry* **186**:364–366.

Craddock N, O'Donovan MC, Owen MJ (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet* **42**:193–204.

de Leon J (2006). AmpliChip CYP450 test: personalized medicine has arrived in psychiatry. *Expert Rev Mol Diagn* **6**:277–286.

Evans L, Akiskal HS, Keck PE Jr, McElroy SL, Sadovnick AD, Remick RA, Kelsoe JR (2005). Familiality of temperament in bipolar disorder: support for a genetic spectrum. *J Affect Disord* **85**:153–168.

Freimer N, Sabatti C (2003). The human phenome project. *Nat Genet* **34**:15–21.

Garraway LA, Widlund HR, Rubin MA, Getz G, Berger AJ, Ramaswamy S, *et al.* (2005). Integrative genomic analyses identify MITF as a lineage survival oncogene amplified in malignant melanoma. *Nature* **436**:117–122.

Glatt SJ, Everall IP, Kremen WS, Corbeil J, Sasik R, Khanlou N, *et al.* (2005). Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. *Proc Natl Acad Sci USA* **102**:15533–15538.

Kelsoe JR, Niculescu AB 3rd (2002). Finding genes for bipolar disorder in the functional genomics era: from convergent functional genomics to phenomics and back. *CNS Spectr* **7**:215–226.

Lasky-Su JA, Faraone SV, Glatt SJ, Tsuang MT (2005). Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. *Am J Med Genet B Neuropsychiatr Genet* **133**:110–115.

Lewinsohn PM, Shankman SA, Gau JM, Klein DN (2004). The prevalence and co-morbidity of subthreshold psychiatric conditions. *Psychol Med* **34**: 613–622.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, *et al.* (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* **353**:1209–1223.

Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, *et al.* (2005). MicroRNA expression profiles classify human cancers. *Nature* **435**:834–838.

MacKinnon DF, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, *et al.* (2002). Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry* **159**:30–35.

Malhotra AK, Murphy GM Jr, Kennedy JL (2004). Pharmacogenetics of psychotropic drug response. *Am J Psychiatry* **161**:780–796.

Moffitt TE, Caspi A, Rutter M (2005). Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry* **62**:473–481.

Niculescu AB 3rd, Akiskal HS (2001). Proposed endophenotypes of dysthymia: evolutionary, clinical and pharmacogenomic considerations. *Mol Psychiatry* **6**:363–366.

Niculescu AB 3rd, Segal DS, Kuczenski R, Barrett T, Hauger RL, Kelsoe JR (2000). Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiol Genomics* **4**:83–91.

Niculescu AB (2004). Genes and bipolar disorders. *The Journal of bipolar disorders* **3**:10–11.

Niculescu AB, Lulow LL, Ogden CA, Le-Niculescu H, Salomon DR, Schork NJ, *et al.* (2006). PhenoChipping of psychotic disorders: a novel approach for deconstructing and quantitating psychiatric phenotypes. *Am J Med Genet B Neuropsychiatr Genet* **141**:653–662.

Nurnberger JI Jr (2002). Implications of multifactorial inheritance for identification of genetic mechanisms in major psychiatric disorders. *Psychiatr Genet* **12**:121–126.

Ogden CA, Rich ME, Schork NJ, Paulus MP, Geyer MA, Lohr JB, *et al.* (2004). Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. *Mol Psychiatry* **9**:1007–1029.

Pages F, Berger A, Camus M, Sanchez-Cabo F, Costes A, Molidor R, *et al.* (2005). Effector memory T cells, early metastasis, and survival in colorectal cancer. *N Engl J Med* **353**:2654–2666.

Pien HH, Fischman AJ, Thrall JH, Sorensen AG (2005). Using imaging biomarkers to accelerate drug development and clinical trials. *Drug Discov Today* **10**:259–266.

Post RM, Ketter TA, Pazzaglia PJ, Denicoff K, George MS, Callahan A, *et al.* (1996). Rational polypharmacy in the bipolar affective disorders. *Epilepsy Res Suppl* **11**:153–180.

Prathikanti S, Weinberger DR (2005). Psychiatric genetics-the new era: genetic research and some clinical implications. *Br Med Bull* **73–74**:107–122.

Preston GA, Weinberger DR (2005). Intermediate phenotypes in schizophrenia: a selective review. *Dialogues Clin Neurosci* **7**:165–179.

Rutter M, Moffitt TE, Caspi A (2006). Gene–environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatry* **47**:226–261.

Schuckit MA, Tipp JE, Bucholz KK, Nurnberger JI Jr, Hesselbrock VM, Crowe RR, Kramer J (1997). The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. *Addiction* **92**:1289–1304.

Schulze TG, McMahon FJ (2004). Defining the phenotype in human genetic studies: forward genetics and reverse phenotyping. *Hum Hered* **58**:131–138.

Segman RH, Shefi N, Goltser-Dubner T, Friedman N, Kaminski N, Shalev AY (2005). Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors. *Mol Psychiatry* **10**:500–513, 425.

Tandon R, Fleischhacker WW (2005). Comparative efficacy of antipsychotics in the treatment of schizophrenia: a critical assessment. *Schizophr Res* **79**:145–155.

Tsuang MT, Nossova N, Yager T, Tsuang MM, Guo SC, Shyu KG, *et al.* (2005). Assessing the validity of blood-based gene expression profiles for the classification of schizophrenia and bipolar disorder: a preliminary report. *Am J Med Genet B Neuropsychiatr Genet* **133**:1–5.

Vogelstein B, Kinzler KW (2004). Cancer genes and the pathways they control. *Nat Med* **10**:789–799.

Volavka J, Czobor P, Cooper TB, Sheitman B, Lindenmayer JP, Citrome L, *et al.* (2004). Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychiatry* **65**:57–61.