

Genetic and Cultural Aspects of Psychotropic Medications

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Genetic Testing

- Our understanding of genetic variation and our ability to rapidly test for common variations in genes (alleles) has enabled us to look screen for differences in the ability to metabolize medication. These tests are expensive but increasingly available.
- What is their usefulness, and what underlying problems might they pose?

Impact of Gender

- The following can effect the appropriate dosage of medication by a factor of 10:
 - Age, concurrent disease, other medications
 - Height, weight
 - Lean/fat ratio
 - Diet
 - Exercise
 - Smoking
 - Alcohol use
- Men and women are different in most of these characteristics. Most research uses male subjects.

Gender and Medication

- Antidepressants
 - No apparent gender effects
- Antipsychotics
 - Women respond better during first episode of illness and require half as much medication as men for maintenance. Because they have higher fat content, long-acting injections should be given less frequently.

Gender and Medication

- Anti-epileptic drugs (AED's):
 - Drugs that induce cytochrome P450 speed up metabolism of oral contraceptives and increase failure 5x. (phenytoin, carbamazepine, phenobarbital, oxcarbamazepine)
 - Drugs that inhibit P450 increase levels of androgens and increase risk of PCOS - Polycystic Ovary Syndrome (valproate)
 - Phenobarbital, carbamazepine, valproate increase risk of osteoporosis, even in men and children

Gender and Medication

- Pregnancy
 - All psychoactive drugs pass through the placenta. All are secreted in breast milk. No drug is safe.
 - Avoid drugs completely in weeks 6-10, if possible.
 - AED's and lithium are problematic.
 - 50% of all pregnancies in the US are unplanned.
 - Mental illness in the mother is detrimental to the fetus.
- Side effects
 - Dystonia occurs more in women, TD in elderly men.
 - Women are more likely to gain weight.

Pharmacogenomics

- Certain variations in genes affect the metabolism of medications. If the metabolism is slowed down, too much drug can accumulate and may be fatal. If metabolism is speeded up, the drug may not be effective at normal doses.
- The cytochrome p450 family of genes, expressed primarily in the liver, affect psychotropic and other medications. There are three main ones:
 - CYP3A4 - lots of drug effects, few polymorphism
 - CYP2D6 - lots of drug effects, lots of polymorphism
 - CYP2C19 - few effects, lots of polymorphism

CYP 2D6

Amphetamines
Aripiprazole (Abilify)
Clozapine (minor) (Clozaril)
Codeine to morphine
Dextromethorphan
Haloperidol (Haldol)
Hydrocodone to hydromorphone
Methadone
Metoprolol
Phenothiazines
Propranolol
Risperidone (Risperdal)
Tamoxifen
Tricyclic Antidepressants
Venlafaxine (Effexor)

CYP 2D6

- Inhibitors
 - Bupropion (Wellbutrin)
 - Cimetidine
 - Duloxetine (Cymbalta)
 - Fluoxetine (Prozac)
 - Haloperidol (Haldol)
 - Paroxetine (Paxil)
 - Phenothiazines
 - Pimozide (Orap)
 - Sertraline (Zoloft)
 - Tricyclic Antidepressants
- Inducers - none

2C19

- Citalopram (Celexa)
- Clozapine (Clozaril)
- Diazepam (Valium)
- Omeprazole (Prilosec)
- Phenytoin (Dilantin)
- Progesterone
- Tertiary amine TCA's

2C19

- Inhibitors
 - Carbamazepine (Tegretol)
 - Cimetidine
 - Disulfiram (Anabuse)
 - Fluoxetine (Prozac)
 - Modafinil (Provigil)
 - Omeprazole (Prilosec)
 - Oxcarbazepine (Trileptal)
 - Topiramate (Topamax)
- Inducers
 - Phenobarbital
 - Phenytoin (Dilantin)
 - Prednisone

The Tests

- Many available on the *Internet*.
- Roche Pharmaceuticals AmpliChip:
 - \$400/test, expect it to generate \$100-150 million a year by 2008.

Ethical Issues

- Justice: distributive justice, access to other genetic services
- Quality: quality control, direct-to-consumer advertising
- Racial Profiling

Racial Profiling

- Is race a relevant variable for mental health practice - diagnosis, treatment?
- In June 2005, the FDA granted BiDil a specific indication for treatment of heart failure in patients who identify themselves as black - our first ethnic medicine.
- For race-based niche marketing to work, it will first have to explore how blacks, whites, Asians, and Native Americans are biologically different.

Racial Profiling: Recent History

- Discrimination by race was discredited in the aftermath of the American and Nazi eugenics programs. In 1998, the Am Anthropological Assoc declared race a “social invention.” In 2000, the Human Genome Project revealed that all humans share 99.9% of the same genes.
- However, in 2005, the first draft of the HapMap noted that a handful of alleles was able to distinguish 3 racial groups: African, Asian, white American. The FDA has also required that different races be included in drug studies.

Racial Profiling

- One reason to focus on the genetics of race is to make inroads in health disparities: blacks tend to do worse in life expectancy, infant mortality, and some chronic diseases than whites. (The best correlate of HTN is darkness of skin.) Many factors account for this, but some geneticists think that genes are partly responsible. Social scientists believe that genetic explanations will obscure the social and economic causes.

Racial Profiling: Practical Observations

- Race-based medication is a convenient compromise until we can inexpensively sequence everyone’s genome.
- It’s also faddish: “Recreational genomics” Internet companies will tell you from a cheek swab how much of your genome is black, white, American Indian, or Asian.

Racial Profiling: Rebuttal

- Self-reports of race do not correspond well to genetic findings. People tend to change their self-identification with race over time.
- Individuals within a racial group differ.
- What racial differences exist are not relevant for most patients. And they pale in the face of differences in lifestyle and medication adherence.

Racial Profiling: Rebuttal

- Genetic variations seem to cluster differently for people with different continents of origin, but is this race? Race is largely dependent on social context. Tutsi and Hutu are different races only in Rwanda, not the United States.
- Might biological measurements of racial differences lead to pronouncements about inherent differences in complex traits, such as intelligence, athletic ability, aggression, susceptibility to addiction?

EthnoPsychoPharmacology

Mrs. Lin

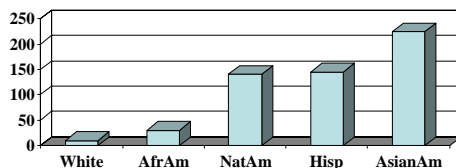
- Mrs. Lin sees her doctor requesting help for difficulty with sleep, appetite, and energy. She has headaches, dizziness, and fatigue. She feels joyless, anxious, and wishes she were dead. She regards her life as a failure.
- Mrs. Lin believes her problem is “neurasthenia” (exhaustion, weakness, diffuse bodily complaints) and if this physical problem could be fixed, she would feel more hopeful and better able to cope.

Mrs. Lin

- Mrs. Lin’s psychiatrist diagnosis a major depressive disorder. He sees the problem as primarily emotional and if the depression is treated, the physical symptoms will improve. He recommends an antidepressant.
- Mrs. Lin’s Chinese psychiatrist disagrees. He sees her as depressed, but sees her problem as neurasthenia -caused by inadequate physical energy in the central nervous system. He recommends a regimen of herbs and other remedies.

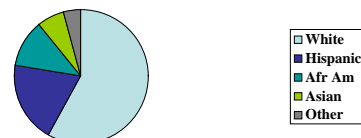
Why Care About Culture?

Percentage Growth in US: 1980-2000



Why Care About Culture?

Percent of US Population: 2050



Why Care About Culture?

- Four states now have white minorities:
 - California
 - Hawaii
 - New Mexico
 - Texas
- 40% of psychiatrists-in-training are now foreign born.

Why Care About Culture?

- Communication
 - Verbal
 - Nonverbal
 - Expectations
 - Interactions
- Accurate diagnosis
 - Illness and culture are complexly intertwined
- Appropriate treatment
 - Strengths, vulnerabilities, conflicts
- Treatment adherence

Impact of Being a Minority in the US

- Child development:
 - Low self-esteem
 - Low motivation and aspirations
 - High vulnerability to antisocial and disruptive behavior
- Less access to mental health services
- Poorer quality care
- Under-representation in research studies

Impact of Being a Minority in the United States

- Increase in depression overall for minorities, immigrants, and refugee (but with less prevalence of guilt as a symptom)
- Increase in depression over time (3% in Mexican Americans immigrants, 14% in 2nd generation Mexican Americans)

Disparities in Treatment and Mental Health Problems

- Difficulty with treatment engagement and retention
- Misdiagnosis of schizophrenia in African Americans and depression in Latinos
- Use of FGA's in African Americans
- High rates of substance abuse and suicide in Native Americans

Disparities in Health Care and Needs

- Life expectancy is lower and infant mortality higher in African Americans
- Diabetes is endemic among African Americans, Latinos, and Native Americans.
- Under-referral to psychiatric care

History

- In the early 20th Century, as clinical syndromes were described in the West, forms of mental illness were searched for throughout various cultures under the rubric of “scientific universalism.”
- However, in the second half of the 20th Century, sociologists and anthropologists argued that mental illness was a social construct.

History

- Mainstream psychiatry continued to insist that culture was simply a confounding variable in understanding mental disorder, which was fundamentally biological.
- Recently, in mental health, however, much has been learned about the impact of culture on diagnosis, therapy, psychopharmacology, and the delivery of mental health services. So there is more openness that culture may make a difference.

History

DSM-IV-TR

- In *DSM-IV* (1994), for the first time, cultural factors were included in the diagnosis and evaluation of mental disorders.
- There are 7 pages (out of 941) devoted to culture, divided into two sections:
 - Outline for Cultural Formulation
 - Glossary of Culture-Bound Syndromes (Culture-bound syndromes are clusters of symptoms and behaviors that are considered by a particular cultural group to be an illness.)

Cultural Explanations of the Individual's Illness

- How and why one becomes ill.
- What symptoms are acceptable in a particular culture?
- What is the appropriate treatment and the prognosis?

Cultural Explanations of the Individual's Illness

- Rapport comes about as the client feels understood and the conversation is in terms that are comfortable to him. With rapport, more sensitive items can be discussed, and a treatment plan can be formulated which has a chance of being followed.

Common Explanatory Models of Illness

- Moral
- Spiritual/ Religious
- Magical
- Medical
- Psychosocial stress

Steps in Seeking Health Care

- Personal awareness that something is wrong
- Labeling the sufferer as “ill.”
- Advice is sought from family, friends, professional and traditional practitioners
- 70-90% of episodes of sickness are managed outside the formal healthcare system - self-treatment, family care, religious practitioners, self-help groups, healers, etc.

Cultural Construction of Clinical Reality

- Through diagnostic activities and labeling, healthcare providers negotiate with patients medical reality, which becomes the object of attention and treatment. Patient-doctor interactions are transactions between explanatory models.

Seeking Health Care

- For many chronic problems, patients' reported improvement may be greater after encounters with alternative practitioners than modern physicians. They feel better even in the absence of improvement of measurable symptoms. This is due in part to closer social class between patient and practitioner, and greater concordance of explanatory systems. (e.g. Chiropractors are more interested in the illness problems and provide an explanatory model that conforms to popular belief.)

Seeking Health Care: Disease vs. Illness

- Disease in the Western view is malfunctioning of biologic processes.
- Illness is the personal, interpersonal, and cultural reactions to disease or discomfort.
- Illness is shaped by cultural factors: perception, labeling, explanation, values

Illness

- Illness is culturally shaped - how we perceive and react to illness is based on our expectations, beliefs, and our social positions. It affects how we communicate about our health problems, how we present our symptoms, when we go for care, whom we go to, how long we stay in care, and how we evaluate our care.
- We learn approved ways of being ill.

Western Culture and Mental Illness

- Many, perhaps all, of *DSM-IV* diagnostic categories are ethnocentric.
- We have hard time seeing this because we believe that we are the reference point for normalcy, morality, and true knowledge - the progress of humanity and psychological understanding has culminated here in Western Culture.

DSM-IV: The Other Culture-Bound Syndromes

- Anorexia nervosa and bulimia
- Dependent personality disorder
- Dissociative identity disorder
- Narcissistic personality disorder
- Gender identity disorder
- Factitious disorder
- Premature ejaculation, anorgasmia

Somatization

- The transformation of personal distress into somatic complaints is the norm in most cultures. In all cultures, patients tend to develop symptoms that are “medically correct” - symptoms that physicians expect and understand.
- Worldwide, the most common somatic complaints are GI and skin sensations. (In the US, gynecological, GI and cardiac complaints are more common.)

Somatization

- Latinos, especially Puerto Ricans and Central American immigrants have the highest rates of somatization.

Stigma

- In most cultures (except Japan, maybe Chinese), there is a much greater stigma against mental illness than in Western European culture.

Response to Psychotropic Medication

- Most minority cultures are more sensitive to the effects and side effects of psychotropic medication. There have been almost no studies that include minority populations.

Ethnopsychopharmacology

- Number of participants in studies of antidepressants over the last ~10 years:
 - 9,327
- Number of Native Americans involved in studies of antidepressants in the last ~10 years:
 - 0
 - Hispanic: 2
 - Asian: 3

Ethnopsychopharmacology

- A large amount of variation has been reported in the response to psychotropic medication in recent years. This may be due to differences to ethnic-specific polymorphic variability, which effect drug metabolism.
- Nonbiologic factors such as age, gender, diet, and smoking also play a role in determining differential response.

Ethnopsychopharmacology

- More than 33% of African Americans and Asians have reduced CYP2D6.
- 10% of Mediterraneans, 20% of Saudi Arabians, and 30% of Ethiopians are rapid CYP2D6 metabolizers.
- 25% of Asians lack a gene for CYP2C19.
- Red blood cell to plasma ratio is different in African Americans and lithium levels are incorrect - they require lower dosages/lower levels for a therapeutic effect.

Ethnopsychopharmacology

- Diet (garlic, onions, blackened fish, corn) may effect the cytochrome function.
- Herbal remedies may also effect cytochrome function.

Antidepressants

- Minorities are rarely included in controlled clinical trials for antidepressants.
- African-Americans are less likely to receive antidepressants than whites. They are more likely to receive TCA's than newer antidepressants. They may have a faster more therapeutic response to TCA's, as well as more delirium. This may be the result of differential metabolism.

Antidepressants

- Asians have slower metabolism of TCA's.
- In one study, hispanics responded to half the dosage of whites, and reported more side effects.
- Very little is known about newer antidepressants.

Antipsychotics

- Asians have higher blood levels of haloperidol on the same dosage compared with whites. They respond better at lower blood levels.
- There appear to be gaps in prescribing newer antipsychotics, especially for African Americans.
- Asians respond to lower levels of clozapine, and may be more likely to experience agranulocytosis. African Americans may have lower baseline WBC, making it difficult for them to take clozapine.

Antipsychotics

- Asians respond to lower levels of risperidone and olanzapine. The same may be true of Hispanics.
- African Americans and Hispanics have greater risk for developing metabolic syndrome for unknown reasons.

Benzodiazepines

- Asians and African Americans have been shown to exhibit more sensitivity to dosage and side effects.

Conclusions

- Where only disease, not illness, is treated, care will be less satisfactory to the patient and less clinically effective than when both disease and illness are treated together.
- Poor care and compliance often is the result of a differing view of clinical reality by patient and treater.
- In defense of Western medicine, it may be true that only modern Western health professionals are capable of potentially treating both disease and illness.

Conclusions

- Clinicians need to elicit the patient's model of illness, explain the clinician's own model, compare, and negotiate a shared viewpoint. This includes:
 - Etiology
 - Onset of symptoms
 - Pathophysiology
 - Course
 - Treatment

Conclusions

- Questions that may help uncover important information:
 - What do you think has caused your problems?
 - Why do you think it started when it did?
 - What do you think your sickness does to you? What are the problems it has caused for you?
 - How severe is your sickness? What do you fear most?
 - What kind of treatment do you think you need?