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PharmGenEd™: Bridging the Gap Between Science & Practice

Train-the-Trainer Session
for Psychiatry I: Depression

Thursday, October 21st, 2010

UNIVERSITY of CALIFORNIA, SAN DIEGO
SKAGGS SCHOOL of PHARMACY
and PHARMACEUTICAL SCIENCES

Disclaimer

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Train-the-Trainer Agenda

1. Introduction
   - Objective of PharmGenEd™ program
   - Shared curriculum and format
   - Introduction of author
2. Review of educational content for selected therapeutic area
3. Future webinar dates
   - Program implementation
   - Other therapeutic areas
4. Contact information
5. Survey instruments
   - Post training survey for trainers
6. Question & Answer (Q & A) session

Overall Objective of PharmGenEd™ Program

- The "Pharmacogenomics Education Program: Bridging the Gap between Science and Practice" (PharmGenEd™) is an evidence-based pharmacogenomics education program designed for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals.
- The overall objective of the PharmGenEd™ program is to increase awareness about current knowledge of the validity and utility of pharmacogenomic tests and the potential implications of benefits and harms from use of the tests.

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Shared Curriculum

- Educational Materials (each 1 hour)
  - Asthma
  - Cardiology I (warfarin & statins)
  - Cardiology II (clopidogrel & beta blockers)
  - Concepts and clinical applications
  - Economic issues
  - Oncology I (solid tumors)
  - Oncology II (hematologic malignancies)
  - Psychiatry I (depression)
  - Psychiatry II (antipsychotics)
- Future webinar dates for these sessions will be provided later

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Therapeutic Area Discussion

- Format
  - Patient case
  - Gene/Allele of interest
  - Functional effect
  - Population prevalence
  - Clinical relevance (dosing/selection, efficacy, and toxicity)
  - Genomic test and testing recommendation
  - Patient case summary

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Learning Objectives

- Upon completion of this program, participants will be able to:
  - Identify specific drug therapies in which pharmacogenomic testing can be applied in the clinical setting
  - Summarize evidence-based recommendations for pharmacogenomic testing
  - Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence

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Antidepressant Medications

- Primary Indications
  - Major depressive disorders (MDD), obsessive-compulsive disorder (OCD), and anxiety disorders
- Pharmacogenomic studies
  - Response in major depressive disorders
  - Side effects
    - Medication intolerance, sexual dysfunction, gastrointestinal (nausea and vomiting)

Davidson 2010, Schosser et al 2009

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Patient Case

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Patient Case

- 25 year old African-American female student who was referred to the clinic by her faculty advisor after requesting to leave school
  - CC: “I’m sad. I can’t do it anymore.”
  - Vitals
    - Weight: 68 kg, Height: 5’8”
    - BP: 108/70, HR: 68
  - HPI (over 3 months): Depressed mood, loss of interest in usual activities, low energy, poor sleep, past thoughts about killing herself but no current suicidal ideation
  - Diagnosis: MDD, Hamilton Rating Scale for Depression (HAM-D) score at clinic visit: 20

Furukawa 2010, Hamilton 1960

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Patient Case Treatment

- Family History:
  - Mother: Currently being treated for depression (medication name unknown)
    - Many people in her family are "sensitive" to medications
- After 8 weeks of treatment with paroxetine 20 mg/day
  - patient is doing much better (HAM-D = 12)
  - she has significant sexual dysfunction (anorgasmia) and asks if there is anything that can be done about this

Cavallari et al 2008, Gavnes et al 2009, Kurian et al 2009, Shern et al 2009

Patient Case (continued)

- Since she has done so well on paroxetine, patient states that she DOES NOT want to discontinue paroxetine.
- Bupropion 150mg/day is used for augmentation of paroxetine and sexual dysfunction
- After 3 weeks of treatment, she complains that her sexual dysfunction has become much worse along with significant nausea. She also feels that her depressive symptoms are getting worse.

Safarineiad 2010, Teter et al 2008

Patient Case (continued)

- Nine weeks after starting treatment, paroxetine and bupropion are discontinued
- So why would patient's sexual dysfunction and nausea get worse?
- The decision is made to start venlafaxine since it has a different mechanism of action

Patient Case (continued)

- Six weeks after starting venlafaxine, there is no improvement (HAMD = 15)
  - Patient is very frustrated and she is genotyped for the CYP2D6 enzyme
  - Test results show that patient is an intermediate metabolizer
- Venlafaxine is discontinued and patient is started on citalopram 20 mg QD
  - Patient eventually goes into remission
  - There is no recurrence of sexual dysfunction

Patient Case Questions

- Questions related to this case
  - Given that we now know she is a CYP2D6 intermediate metabolizer, does this explain anything in her past treatment?
  - If we have had this information at the beginning of treatment, how might it have changed practice and the patient's response?

De Leon 2007

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Treatment of Depression

Antidepressant Classes:

1. Selective Serotonin Reuptake Inhibitors (SSRI)
2. Serotonin Norepinephrine Reuptake Inhibitors (SNRI)
3. Tricyclic Antidepressants (TCA)
4. Monoamine Oxidase Inhibitors (MAOI)
5. Miscellaneous Agents: Trazodone, Nefazodone, Mirtazapine, and Bupropion

Teter et al 2008

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Treatment of Depression

- First line treatment of MDD
  - Stage 0: Patient assessment and discussion of options including non-pharmacologic treatment
  - Stage 1: SSRI, bupropion, mirtazapine, SNRI as monotherapy
  - Stage 1: Partial Response – augment with additional agent
  - Stage 2: Non response – switch to a different class of antidepressant

TMAP 2010

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Pharmacogenomics of Antidepressants

- Pharmacodynamic Effects
  - Variants associated with response are often associated with the pharmacology of antidepressants
    - Variants within the serotonin neurotransmitter system (receptors or transporters)
- Pharmacokinetic Effects
  - Variants associated with side effects are often associated with the metabolism of antidepressants
    - Variants within the cytochrome P450 system or drug transporter

Kirchheiner et al 2010, Zandi et al 2010, Zhou 2009

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Antidepressant Pharmacology

- Inhibit serotonin (5-HT) reuptake via serotonin transporter antagonism
  - All SSRIs and SNRIs, most TCAs
- Block norepinephrine (NE) reuptake
  - All TCAs and SNRIs
- Block dopamine (DA) reuptake
  - *Weak reuptake of* bupropion.....also sertraline
- Block NE, 5-HT, DA metabolic pathways
  - MAOIs
- Block postsynaptic 5-HT/NE receptors
  - Mirtazapine, nefazodone, trazodone

Teter et al 2008

Pharmacodynamic Candidates

- Antidepressants have antagonistic effects at other receptors
  - Serotonin 2 and 3 (HTR2 and HTR3) receptors
  - Alpha 1 and 2 (α1 and α2) receptors
  - Histamine 1 (H1) receptors
  - Cholinergic (Ach) receptors
- Antagonism at these receptors may be associated with response and side effects

Teter et al 2008

Pharmacodynamic Candidates

- Neurotransmitter systems
  - Serotonin
- Other miscellaneous growth factors and enzymes
  - Tryptophan hydroxylase 1 (TPH1)
  - Monoamine oxidase (MAO)
  - G-protein β-3 subunit (GNB3)
  - Brain-derived neurotrophic factor (BDNF)

Kato et al 2010

Response in Depression

- Gene/Allele
  - Serotonin Transporter (*SLC6A4,* 5HTTLPR, 17q11.1-q12)
    - 44 base pair insertion deletion that may involve *SLC6A4* expression – results in a *long (l)* and *short (s)* allele
  - Variable number of tandem repeats (VNTR) within intron 2 (STin2)
    - May contain 9, 10 or 12 copies of 16-17 bp repeat

Kato et al 2010, Serretti et al 2007

Response in Depression

- Gene/Allele
  - Serotonin-5HT1A receptor gene *(HTR1A)* (5q11.2-13)
    - -1019C/G (rs6295)
    - For the HTR1A variants, the G allele results in reduced serotonergic neurotransmission
  - Serotonin-5HT2A receptor gene *(HTR2A)* (13q14-21)
    - C102T (rs6313)
    - -1438A/G (rs6311)
    - For the HTR2A variants, these variants are in complete linkage disequilibrium

Kato et al 2010, Serretti et al 2007

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Response in Depression

- Gene/Allele
  - Serotonin Biosynthesis
    - Tryptophan Hydroxylase 1 (*TPH1*) (11p15.3-p14)
      - 218 A/C
      - 779 A/C
    - Tryptophan Hydroxylase 2 (*TPH2*) (12q21.1)
      - 1463 G/A (Arg441His)
      - Arg447Pro
      - rs1843809, rs1386492, rs1487276

Kato et al 2010, Serretti et al 2007

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Response in Depression

- Gene/Allele
  - Monoamine Catabolism
    - Monoamine Oxidase A (*MAOA*) (Xp11.23)
      - VNTR
  - Serotonin Receptor Second Messenger
    - G protein β-3 subunit (*GNB3*) (12p13)
      - 825C/T (rs5443)
  - Growth Factors
    - Brain Derived Neurotrophic Factor (*BDNF*) (11p13)
      - Val66Met (rs6265)

Kato et al 2010, Serretti et al 2007

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Response in Depression

- Functional Effect
  - Serotonin Transporter (*SLC6A4,* 5HTTLPR, 17q11.1-q12)
    - *L* allele has twice the *SLC6A4* expression than the *s* allele
  - STin2
    - May also affect *SLC6A4* transcription and may be synergistic with 5-HTTLPR
- Population Prevalence
  - Serotonin Transporter (*SLC6A4,* 5HTTLPR, 17q11.1-q12)
    - The L allele is present in about 50-60% of the Caucasian population, and 30-40% in Asian populations
  - STin2
    - The 10 and 12 alleles has allele frequencies of 10-20% and 80-90% respectively within the Asian population

Johns Hopkins University 2010, Kato et al 2010, Serretti et al 2007

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Response in Depression

- Functional Effect
  - Serotonin-5HT1A receptor gene *(HTR1A)* (5q11.2-13)
    - -1019C/G (rs6295)
      - The G allele results in reduced serotonergic neurotransmission
  - Serotonin-5HT2A receptor gene *(HTR2A)* (13q14-21)
    - C102T (rs6313)
    - -1438A/G (rs6311)
      - The -1438 A allele has been associated with significantly increased promoter activity compared to the G allele. However, not all studies have confirmed this
- Population Prevalence
  - Serotonin-5HT1A receptor gene *(HTR1A)* (5q11.2-13)
    - -1019C/G (rs6295)
      - Present in 50% of Caucasians and 21% of Asians
  - Serotonin-5HT2A receptor gene *(HTR2A)* (13q14-21)
    - C102T (rs6313)
    - -1438A/G (rs6311)
      - Present in about 50% of the population.

Kato et al 2010, Serretti et al 2007

Response in Depression

- Functional Effect
  - Tryptophan Hydroxylase 1 (*TPH1*) (11p15.3-p14)
    - 218 A/C
    - 779 A/C
  - Tryptophan Hydroxylase 2 (*TPH2*) (12q21.1)
    - 1463 G/A (Arg441His)
    - Arg447Pro
    - rs1843809, rs1386492, rs1487276

Kato et al 2010, Serretti et al 2007

Response in Depression

- Functional Effect
  - Monoamine Catabolism
    - Monoamine Oxidase A (*MAOA*) (Xp11.23)]: VNTR 3.5 and 4 repeats have been found to be longer and are felt to be more functional than the 3 and 5 repeats
  - Serotonin Receptor Second Messenger
    - G protein β-3 subunit (*GNB3*) (12p13)]: 825 C/T (rs5443)
  - Growth Factors
    - Brain Derived Neurotrophic Factor (*BDNF*) (11p13): Val66Met (rs6265)
- Population Prevalence
  - Monoamine Catabolism
    - VNTR: 3 repeats (36%), 3.5 repeats (9%), 4 repeats (56%), 5 repeats (<2%) in Caucasians
  - Serotonin Receptor Second Messenger
    - 825C/T (rs5443): The T allele is present in about 30-60% of Caucasian, Asian, and African populations
  - Growth Factors
    - Val66Met (rs6265): The A (Met) allele is present in about 20% of the Caucasian population and 60% of the Asian populations

Kato et al 2010, Serretti et al 2007

Antidepressant Pharmacokinetics

- Most of the antidepressants are metabolized by cytochrome P450 (CYP450) enzyme pathways
  - We have the most information about these pathways
    - Located primarily in the smooth endoplasmic reticulum in liver (also intestinal wall, kidney, nasal epithelium, lung, and brain)

Bertilsson 2007

P450s and Drug Metabolism

Enzyme	Fraction of Drug Metabolism
CYP3A4	40-45%
CYP2D6	20-30%
CYP2C9	10%
CYP2C19	5%
CYP1A2	5%
CYP2E1	2-4%
CYP2A6	2-4%
CYP2C8	2%

Daly et al 1996, Ingleman-Sundberg 2004, Oscarson et al 2002

Antidepressant Substrates of P450s

CYP1A2	CYP2B6	CYP2C19	CYP2D6	CYP3A4
clomipramine	bupropion	clomipramine	all TCAs	Amitriptyline
imipramine		amitriptyline	atomoxetine	Clomipramine
amitriptyline		imipramine	paroxetine	Imipramine
fluvoxamine		citalopram	venlafaxine	Trazodone
mirtazapine			duloxetine	
			sertraline	
			fluoxetine	
			mirtazapine	

Flockhart DA. *Drug Interactions: Cytochrome P450 Drug Interaction Table.* Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table/asp Accessed [August 1, 2010].

Antidepressant Inhibitors for CYP450

Drug	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram Escitalopram	**----**	**----**	**----**	**+/-**	**----**
Fluoxetine	**----**	**+/-**	**+++**	**+++**	**+**
Fluvoxamine	**+++**	**+**	**++**	**+/-**	**++**
Paroxetine	**----**	**+/-**	**+/-**	**+++**	**----**
Sertraline	**----**	**+/-**	**----**	**+**	**----**
Nefazodone	**----**	**----**	**----**	**----**	**++**
Bupropion	**----**	**----**	**----**	**++**	**----**
Duloxetine	**----**	**----**	**----**	**+**	**----**

---- none or unknown, +/- slight, + low, ++ moderate, +++ potent

Adapted from Kotlyar et al 2005; Spina et al 2008

Pharmacokinetic Candidates

- Gene/Allele
  - CYP2D6 gene is polymorphic
  - This means that it exists in different forms
- Functional Effect
  - These different forms result in different abilities to metabolize drugs that are substrates for this enzyme

De Leon et al 2006

Pharmacokinetic Candidates

- Functional Effect
  - Alterations within the *CYP2D6* gene result in differences in metabolism
  - People can be classified as:
    - Ultra rapid metabolizers (UMs)
    - Rapid (or extensive) metabolizers (EMs)
    - Intermediate metabolizers (IMs)
    - Poor metabolizers (PMs)
  - There are over 78 different variants associated with *CYP2D6* that result in metabolic differences

Zhou 2009

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Pharmacokinetic Candidates

- Population Prevalence
  - Caucasians
    - 5-10% of Caucasians lack enzyme
    - CYP2D6 *1, *3, *4, *5, and 6* are the most common alleles for reduced metabolism
    - The *3 and *4 allele constitute ~75% of alleles responsible for the PM phenotype
  - Asian Populations
    - Most PM phenotypes due to CYP2D6 *10 allele
  - African Populations
    - Most PM phenotypes due to CYP2D6 *17 allele

Bertilsson 2007, Zhou et al 2009

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Pharmacokinetic Candidates

- Population Prevalence
  - People can also exhibit the UM phenotype
    - Most individuals have variants that result in multiple copies of the *CYP2D6* gene resulting in extremely high CYP2D6 activity
    - UMs occur in about 2% of the Caucasian and African American population
    - These gene duplications are often associated with the *1 and *2 allele
      - CYP2D6 *1 x N and CYP2D6 *2 x N

Zhou 2009

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Population Prevalence

Major variant allele	Caucasians (%)	Asians (%)	African-Americans (%)
CYP2C9*2	8-12	<3	<3
CYP2C9*3	6-10	4-7	1-2
CYP2D6*4	12-21	1	2
CYP2D6*5	27	6	4
CYP2D6*10	1-2	51	6
CYP2D6*17	0	0	20-35
CYP2D6*41	8-10	0-2	11-14
CYP3A4*1B	4	0	67
CYP3A5*3	92-94	55-75	29-35
CYP1A2*1F	68	32	46

Modified from Takahashi et al 2001; Lee et al 2002; Ingelman-Sundberg et al 2005, Soyama et al 2005, Xie et al 2004, Sata et al 2000

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Clinical Relevance

- Efficacy
  - 5HTTLPR
    - Meta-analysis of 15 studies (1435 patients)
      - Remission (HAMD < 7)
      - Response (HAMD/MADRS ↓ by 50%)
      - 4 week response rate

Serretti et al 2007

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Clinical Relevance

OR (95% CI)	Total		Caucasian		Asian	
	L carriers vs ss	II vs S carriers	L carriers vs ss	II vs S carriers	L carriers vs ss	II vs S carriers
Remission	2.21* (1.5-3.21)	1.42 (0.9-2.04)	2.37* (1.56-3.6)	1.37 (0.93-2)	1.7 (0.7-3.93)	2.28 (0.59-8.9)
Response	1.20 (0.9-1.6)	2.01* (1.3-2.89)	1.53 (0.9-2.59)	1.74* (1.1-2.76)	1.09 (0.78-1.5)	2.52* (1.37-4.6)
4 week response	1.72* (1.2-2.47)	2.57* (1.7-3.88)	1.37 (0.6-2.88)	1.75* (1.1-2.88	1.85 (0.22-2.8)	5.96* (2.7-13.2)

* = statistically significant

Serretti et al 2007

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Clinical Relevance

- Efficacy
  - Kato and Seretti Meta-Analysis
  - 8 genes examined
    - Significant relationship with response
      - TPH1 218C/C
        - » OR: 1.62, p = 0.005
      - BDNF Val66Met
        - » OR: 1.62, p= 0.02
    - Sample sizes included in analyses were small and need replication

Kato et al 2010, Serretti et al 2007

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Clinical Relevance

- Toxicity
  - Antidepressant Intolerance
    - *CYP2D6*, *HTR2A*, serotonin transporter (5HTTLPR)
      - Murphy et al 2003
      - Murphy et al 2004
      - Murphy 2006
      - Hu et al 2007
  - SSRI-Associated Sexual Dysfunction
    - *HTR2A*, serotonin transporter (5HTTLPR)
      - Bishop et al 2006
      - Bishop et al 2009
  - SSRI-Associated Nausea and Vomiting
    - CYP2D6 and HTR2A
      - Suzuki et al 2006

Hu et al 2007, Murphy 2003, Suzuki 2006

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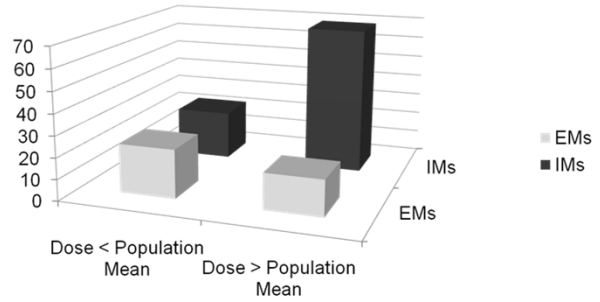
Clinical Relevance

- Toxicity
  - Inpatients treated for MDD (n = 365)
    - 30% received a CYP2D6 substrate
      - 13% of PMs and 36% of IMs treated with CYP2D6 substrate
    - DOTES (Dosage Record and Treatment Emergent Symptoms Scale)
      - PMs = 7.7 ± 4.7
      - Non PMs = 2.0 ± 3.4 (*p = 0.007*)
    - Clinical Global Impressions Scale
      - Response rate in IMs
      - Treated with CYP2D6 drugs = 7%
      - Treated with other medications = 25% (*p = 0.017*)

Laika et al 2009

Clinical Relevance

Percentage of Subjects Experiencing Moderate/Marked Side Effects Stratified by CYP2D6 and Dosage



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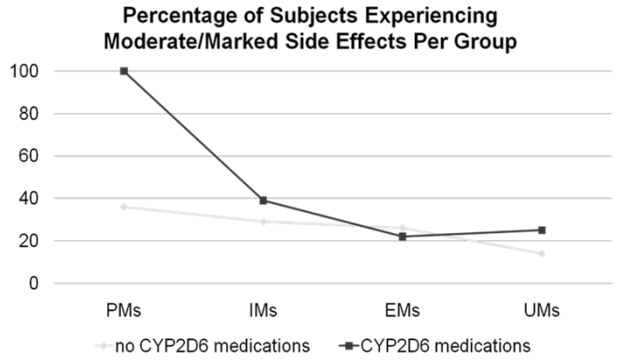
Clinical Relevance

CYP2D6 and Toxicity



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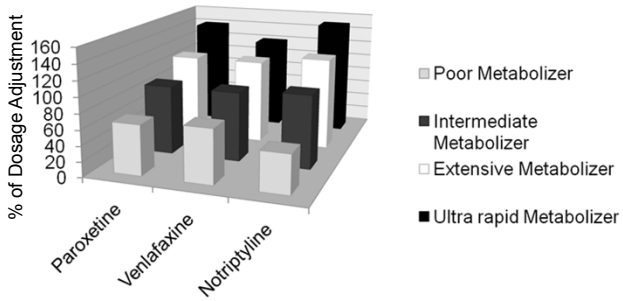
Clinical Relevance

Dosing: Percent Dosage Adjustment Recommendations for Antidepressants based on CYP2D6 metabolic activity



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Pharmacogenomic Test

- No FDA-approved pharmacogenomic test for pharmacodynamic targets
  - Available from selected private and academic laboratories
  - Reimbursement unclear
- There are several FDA-approved pharmacogenomic test for CYP2D6 (and CYP2C19)
  - Despite the availability of this test, it often does not get used clinically
  - Problems concerning the use of the these tests include cost and provider familiarity with test and results
  - Reimbursement may be obtained but coverage is not consistent

De Leon et al 2006

Testing Recommendation

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group Conclusion of literature review and meta-analysis
- "There is a paucity of good-quality data addressing the questions of whether testing for CYP450 polymorphisms in adults entering SSRI treatment for non-psychotic depression leads to improvement in outcomes, or whether testing results are useful in medical, personal, or public health decision making".

EGAPP 2007

Testing Recommendation

- Based on these guidelines, pharmacogenomic testing is not recommended for everyone.
- However, these guidelines do not preclude using pharmacogenomic testing in clinical practice.
- There may be situations in which pharmacogenomic testing may help to guide therapy decisions and prevent the occurrence of side effects and or non-response.

EGAPP 2007, Matcher et al 2007, Teutsch 2009

Case Summary

- As the case pointed out, knowing CYP2D6 genotype information before starting treatment may allow for greater success in treating depression due to the potential for early remission with personalized medicine regimens based on this information.

Kotlyar et al 2005

Summary

- Pharmacogenomic testing as it relates to the treatment of depression
  - Pharmacodynamic
    - Based on medication pharmacology and neurotransmitters related to depression pathophysiology
      - 5HTTLPR
  - Pharmacokinetic
    - Based on medication's absorption, metabolism, distribution, and excretion characteristics
      - CYP2D6

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Summary

- Serotonin Transporter
  - Pharmacodynamic target of many antidepressants
    - 5HTTLPR
      - Also known as serotonin transporter promoter region (SERTPR)
      - Felt to explain about 15% of the variance seen in antidepressant response
      - Most studied and most consistent finding across all pharmacogenomic studies relating to antidepressant response
- Other pharmacodynamic targets have been identified

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Summary

- CYP2D6 is an isoenzyme that is responsible for the metabolism of up to 20% of all medications
  - Within psychiatry, most medications are metabolized by CYP2D6
  - For antidepressants, very few are not metabolized by CYP2D6 and many inhibit this enzyme

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Summary

- Testing for CYP2D6 metabolic capability is commercially available
  - This test is not routinely used due to issues with prescriber familiarity, cost, and insurance reimbursement
    - A recently convened panel of experts (EGAPP) were unable to find data to support its use clinically
    - They emphasized the promise of CYP2D6 testing in major depressive disorder and advised that more research be done.
- While CYP2D6 testing may be important for determining side effects to the antidepressants, there are many other pharmacodynamic targets that also need to be considered.
- Antidepressant response is multi-factorial, with pharmacogenetics playing only one part

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Webinar Dates
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- **Oncology II: Hematologic Malignancies**
  - Tuesday, Aug. 10, 2010 10am-12pm – COMPLETED
- **Concepts and Clinical Applications**
  - Wednesday, Aug. 11, 2010 – COMPLETED
- **Psychiatry II: Antipsychotics**
  - Tuesday, Aug. 24, 2010 10am – 12pm – COMPLETED
- **Oncology I: Solid Tumors**
  - Thursday, Aug. 26, 2010 10 am – 12 pm – COMPLETED
- **Cardiology I: Warfarin and Statins**
  - Tuesday, Sept. 21, 2010 10am –12 pm – COMPLETED
- **Cardiology II: Clopidogrel and Beta Blockers**
  - Thursday, Sept. 23, 2010 10 am – 12 pm – COMPLETED
- **Economic Issues**
  - Tuesday, Oct. 12, 2010 9:30 am – 11:30 am – COMPLETED

Webinar Dates
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- **Psychiatry I: Depression**
  - Thursday, Oct. 21, 2010 10am – 12pm
- **Asthma**
  - Tuesday, Nov. 2, 2010 10am – 12pm
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