Response to drug treatment: prediction in young people

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Is prediction for individuals good enough to use in clinical practice?

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WHY PREDICT RESPONSE?

(A treatment trial will often give a clearer answer than even a “significant” prediction)

• To understand the treatment
• To influence choice of treatment
  - therapy helpful only for a small minority
  - hazardous or expensive therapy
  - many therapies available
• To influence treatment regime
  - dynamics, kinetics, adherence
Predicting: outcome, regime, AEs

- Single dose
- Clinical profile
  - Subtypes
  - Comorbidity
- Pharmacogenomics
- Brain function
- Early response; Compliance

Meta-analyses draw on >300 studies
METHODS OF STUDIES

• Measure the marker at baseline and outcome
• Correlate change in marker with clinical outcome
• Avoid confounders
  - regression to mean, recovery, placebo, fluctuations
• Compare with placebo
  - crossover
  - regression
• Fixed v variable dose; absolute or relative outcome
Baseline predictors of response to fluoxetine in MDD:
family members’ depressive illness: 80% v 55% remitted at 12 weeks;
no prediction from age, sex, ethnicity, MDD episodes, psychiatric comorbidities, length of illness, depression severity, global functioning of the child and family, suicidal behaviors

Prediction from early monitoring

Percent reduction in CDRS-R scores at each week for remitters versus nonremitters. N=168, age 7 - 18
Tao et al JAACAP 48 71-78
Value of a predictive marker

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Treated</th>
<th>Bayes Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pretest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Pretest</td>
<td>100</td>
<td>56</td>
<td>14</td>
</tr>
<tr>
<td>Positive (70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (30)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*but 30 children miss an even chance of improvement - unless alternative works

**So a marker becomes useful if treatment is hazardous; or very costly (or if there are many possible treatments and response is slow)**
Serotonin transporter gene polymorphism and antidepressant response

• The prior probability of non-response to drug treatment in the total group of 120 patients was 27.5%. The posterior probability of non-response increased to 40.4% for patients who lacked the s/s polymorphism in the promoter region (n = 52 patients in this group), and to 83.3% for those who lacked the l/l polymorphism in intron 2 (n = 24 patients in this group).


Under the age of 25 yr the T allele of the G protein β3 subunit was associated with a markedly poorer response to nortriptyline, not fluoxetine; serotonin transporter polymorphisms did not predict antidepressant response. Opposite result in patients >25 yr

Joyce et al 2003 IJNPP 6 339
Predicting antipsychotic effects

-141C Ins/Del in DRD2, Ser9Gly in DRD3, -1438G/A in HTR2A, 5-HTTLPR and Val108Met in COMT.

PMs of CYP2D6 have 43% higher risk of developing TD.

The CATIE GWAS study examined 12 indicators of metabolic side effects of antipsychotic drugs in the same cohort. Multiple SNPs in multiple genes reached genome-wide significance. rs1568679 in Meis homeobox2 mediated the effect of risperidone on waist and hip circumferences, rs13224682 in PRKAR2B (protein kinase cAMP-dependent regulatory type II-β) mediated clozapine and olanzapine's effects on triglyceride levels, G allele of leptin.
FIG. 1. Baseline ABC Irritability subscale score as a moderator of response to risperidone. ABC = Aberrant Behavior Checklist, PBO = placebo, RIS = risperidone, BL = baseline. Lines represent mean ABC Irritability Subscale score at each week by treatment and moderator subgroups.
Predicting weight gain in children treated with antipsychotics

I. CYP2D6 Poor metabolisers responded but gained weight + Rapid metabolisers were nonresponders. Youngster et al 2014 DMCN

II. GWAS

Risk allele homozygotes gained twice as much weight as other patients after 12 weeks of treatment, and the genetic effect was not drug-specific.
Range of ADHD Medication

Methylphenidate, dexamfetamine, atomoxetine; bupropion, clonidine, TCAs

Recently licensed:

Guanfacine

Lisdexamfetamine

Risperidone for “irritability”

International licences now being sought:

Modafinil

Focalin

Coming later: percutaneous delivery; nicotine & GABA analogues; AMPAkines & CREBS?
REVIEW OF PREDICTORS IN ADHD

• Psychophysiology = high or low skin conductance
  normal or abnormal EEG
  high or low heart rate

• Neurology = presence of soft signs

• Familial = good management

• Age = younger or older

• Clinical = high severity: (IQ inconsistent); poor attention

Barkley (1976) Journal of Abnormal Child Psychology
Predict by genetics?

- CYP2D6 polymorphisms for atomoxetine; poor metabolisers (7%) have more AEs – eg double the BP increase
- DRD4.7 findings contradictory
- DAT 10/10 ? predicts nonresponsiveness*
- glutamate receptor 7 gene & NA transporter suggested in genome scan**


Clinical clustering in boys with disruptive behaviour

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Medication response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkinetic</td>
<td>73%</td>
</tr>
<tr>
<td>Conduct</td>
<td>14%</td>
</tr>
<tr>
<td>Anxious/depressed</td>
<td>8%</td>
</tr>
</tbody>
</table>

* “Marked improvement” in drug and not placebo; N=38 in crossover double-blind R.C.T.

What predicts “good response” to MPH?

<table>
<thead>
<tr>
<th>Taylor et al</th>
<th>Buitelaar et al</th>
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</thead>
<tbody>
<tr>
<td>High severity</td>
<td>Low severity</td>
</tr>
<tr>
<td>Low IQ</td>
<td>High IQ</td>
</tr>
<tr>
<td>Young age</td>
<td>Young age</td>
</tr>
<tr>
<td>Low anxiety</td>
<td>Low anxiety</td>
</tr>
</tbody>
</table>
## Differences between studies

<table>
<thead>
<tr>
<th>Taylor et al</th>
<th>Buitelaar et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disruptive behaviour</td>
<td>ADHD</td>
</tr>
<tr>
<td>Optimal dose</td>
<td>Fixed low dose</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>Normalised</td>
</tr>
<tr>
<td></td>
<td>(&quot;improved&quot; was not predicted)</td>
</tr>
<tr>
<td>Crossover placebo</td>
<td>Regression subtraction</td>
</tr>
</tbody>
</table>
Which child shows good response?

Child A

Child B

Normalisation
Moderators of response in MTA

• Response to MED v BEH is smaller in:
  – Anxious children *(doubly comorbid larger)*
• “Excellent” MED response less likely for:
  – Children with depressed mothers
  – Low IQ
  – Children with severe symptoms
• Children in poverty showed decline in parent-child closeness with MED
Subtyping

ANXIETY / DEPRESSION

SCHOOL

HOME

HKD

INAT 6/9

IMP 1/4

HYP 3/5

IMPAIRMENT
Subtyping
ANXIETY / DEPRESSION

SCHOOL
HYP 3/5
HYP 3/5
HYP 3/5
HYP 3/5

HOME
HYP 3/5
HYP 3/5
HYP 3/5
HYP 3/5

IMPAIRMENT
HYP 3/5
HYP 3/5
HYP 3/5
HYP 3/5

INAT 6/9
INAT 6/9
INAT 6/9
INAT 6/9

IMP 1/4
IMP 1/4
IMP 1/4
IMP 1/4

HKD
HKD
HKD
HKD

IMPAI RMENT
SNAP Hyperactivity-Impulsivity (Parent)
SNAP Hyperactivity-Impulsivity (Parent)
SSRS Total Social Skills (Parent)
Treatment decisions

• Severe, pervasive, disabling?
• Problems at home?
• Problems at school?
• Persistent after treatment?
• Comorbid problems?

- Home CBT
- Liaison + self-instruction
- Medication
Outcome and adherence

- Simpson et al BMJ 2006 333 15
  - Metaanalysis: good adherence in about 50%; predicts good outcome, even for placebo. ("healthy adherer")

- Charach et al J Amer Acad CAP 43 559
  - Adherence to stimulants over 5 years predicts good outcome, is predicted by youth, severity of ADHD, no ODD
Conclusions

• Prediction of response depends upon the outcome desired.
• Strongest predictors mostly clinical
• Pharmacogenetics useful for speed of action and choice of antpsychotic
• Future possibilities for genes & MRI