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# Breakout Session 1 –

# Specific Challenges PK / PD

# Recommendations

**Co-chairs:**

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# Recommendations

- Timely evaluation of PK and PD in:
  - Age cohorts from neonates to adolescents
    - Overlapping prospective cohort designs
  - ADME to understand differences in PK
  - Much greater attention to PD endpoints
    - Safety, Cognitive, QEEG, imaging, sleep
  - PK extrapolation from adjunctive therapy to monotherapy

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# Recommendations

- Timely evaluation of PK and PD in:
  - Titration to max dose in MAD trials
  - Safety endpoints
  - Population PK
  - Phase 0 microdosing to get information about target and off target engagement peripherally and centrally
  - Vulnerable subgroups

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# Recommendations

- Randomized controlled trials:
  - Pragmatic trials with long term followup
  - Randomized dose or active controlled trial
  - Randomized multiple baseline withdrawl designs
- Industry: Active post-marketing surveillance: data mining, cohorts, registries
- Practice-based EMR networks using standardized assessments to answer specific questions
- Regulatory: Sentinel Initiative, REMS framework, enabling legislation

# Recommendations PK / PD

- What should we measuring?
  - Phase 1 in pt volunteers
- PD assessments
  - qEEG
  - Neuroimaging
- Limitations of current treatments as monotherapy
  - Promises of improved profile and results not fulfilled
- Unable to predict who will respond to which treatment

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# Recommendations PK / PD

- **The new estimates**
  - **Confirm that disorders of the brain are the major contributor to the total EU disease burden;**
  - **Reveal that depression — in contrast to previous projections - is already now the most important single contributor to the total disease burden;**
  - **Show that there are tremendous diagnosis-specific differences, and highlight that even seemingly "less serious" disorders are associated with a substantial degree of disability**
  - **Confirm the existence of substantially different disability differences between females and males.**

**Ref : ECNP/EBC Report 2011 Eur Neuropsychopharmacology 21, 655-679**

# Mental Health Problems the Statistics

- At least 1 in 4 people will experience a mental health problem at some point in their life and one in six adults has a mental health problem at any one time
- 1 in 10 children aged 5 –16 yrs has a mental health problem, and many continue to have mental health problems into adulthood
- Half of those with lifetime mental health problems first experience symptoms by the age of 14 and three-quarters before their mid-20s
- Self-harming in young people is not uncommon
  - 10–13% of 15–16-year-olds have self-harmed
- Almost half of all adults will experience at least one episode of depression during their lifetime

Ref: No Health without Mental Health Feb 2011

# Recommendations - Pharmacovigilance

- **Four sequential levels of treatment based on Non-remission**
- **Remission rates levels 1 to 4**
  - **36.8%, 30.6%, 13.7%, 13%**
  - **Only 1/3 pts remitted at first treatment level**
  - **Only modest differences between treatments at each subsequent level**
- **Although 67% pts remitted about a half relapsed over a 1 yr follow-up**
  - **Increasing relapse rates at successive levels of care**
  - **40.1%, 55.3%, 64.6%, 71.1%**

**Ref: Rush et al 2006**

# Conclusions from STAR*D

- Depression difficult to treat to remission
- Low Sustained Remission rates that are difficult to maintain with any treatment option or stepped treatment
- High rates of tolerability problems
- Targeting monoamine neurotransmission alone appears insufficient for sustained benefit for most patients

Ref: Shelton et al 2010

# What can we do Better?

- Most chronic diseases consider a "stepped care" model
- Lumping rather than splitting
  - First vs recurrent
  - Genetics
  - Psychiatric vs physical co-morbidity
- Alternative outcomes to mood alone:
  - Emotion, cognition
  - LT effectiveness - function
- What can we learn from research in other indications

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# Augmentation Strategies – Methodology, and Regulatory Perspective

- **Background, Concepts and Definition**
  - **Amir Kalali**
- **Antidepressant Augmentation: Acceleration & Enhancement Strategies**
  - **Sidney Kennedy**
- **Current Examples**
  - **Geoffrey Dunbar, James Youakim, Erik Buntinx**
- **Discussion**
- **Regulatory Forum**

  **FDA: Thomas Laughren**

  **EMA - Karl Broich**
- **Panel Discussion**

  **Schizophrenia: Stephen Marder**
  **Bipolar: Charles Bowden**
  **Cognition: Richard Keefe**
  **Discussant: Sidney Kennedy**