Management of Major Depressive Disorder

Roy Perlis, MD MSc

Center for Experimental Drugs and Diagnostics (CEDD)
Department of Psychiatry
Center for Human Genetic Research
Massachusetts General Hospital

rperlis@partners.org
Disclosure (past year)

• Consulting/Scientific Advisory Boards
  – Proteus Biomedical, Genomind, RIDVentures, First Lab, Pamlab, Healthrageous

• Patents/Royalties
  – Concordant Rater Systems

• Commercial research support
  – Proteus Biomedical

• Non-commercial research support
  – NIMH, NSF, Stanley Center for Psychiatric Research, NARSAD
The good news: Depression treatment has similar outcomes in primary and psychiatric care (STAR*D; N=2876)

Trivedi et al., Am J Psychiatry 2006;163:28-40
The bad news: treatment-resistance is expensive

Total costs increased $1530/year for mild TRD; 1 point=$590  
Gibson AJMC 2010
Depression as a potentially lethal illness

- Mood disorder patients are ~20-30x more likely to die by suicide vs. general population

[Graph showing standardized mortality ratio over years of follow-up for unipolar disorder]
Key questions

• How do I screen?
• When is further workup indicated?
• What is first line treatment?
• What are reasonable next steps?
  – “and what’s with those TV commercials???”
• “But I just prescribe exercise!”
• What about complementary/alternative options?
• Am I missing bipolar disorder?
• A blood test for major depression?
The screens boil down to this:

• “Have you been feeling depressed, or lost interest in things?”

• Consider using the QIDS-SR to characterize severity (16-item self-report checklist; takes 5 minutes…)

• Alternatives: PHQ-9, many others

* www.ids-qids.org; www.depression-primarycare.org/clinicians/toolkits/materials/forms/
Now ~5+ genes for BPD, and counting

None are diagnostic, explain <1% of risk.

PGC-bipolar, Nat Gen 2011
These variations don’t just affect risk for bipolar disorder....

The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia

EK Green¹, D Grozeva¹, I Jones¹, L Jones², G Kirov¹, S Caesar², K Gordon-Smith¹,², C Fraser¹, L Forty¹, E Russell¹, ML Hamshere¹,³, V Moskvina¹,³, I Nikolov¹,³, A Farmer¹, P McGuffin¹, Wellcome Trust Case Control Consortium², PA Holmans¹,³, MJ Owen¹, MC O’Donovan¹ and N Craddock¹

Phenotypic Effects of a Bipolar Liability Gene Among Individuals With Major Depressive Disorder

Francesco Casamassima¹,² Jie Huang,³,⁴ Maurizio Fava²,³,⁴ Gary S. Sachs,²,⁴ Jordan W. Smoller,³,⁴ Giovanni B. Cassano,¹ Lorenzo Lattanzi,⁴ JES Fagerness², Jonathon P. Stange² and Roy H. Perlis²,³,⁴

Diagnostic Products Corp, Los Angeles, CA, USA (control levels = 1.9 ± 1.3 ng/ml). Chromogranin A was measured using a two-site immunoassay kit (ALPCO Diagnostics, Salem, NH, USA) (control levels = 29.6 ± 21.3 ng/ml). Fold change (FC) was calculated as the disease:control ratio of analyte levels. Statistical significance (P-value) was determined by two-tailed t-tests. Significant FC values are indicated in bold font.

disorder patients (Table 1), suggesting that these molecules are not altered in all neuropsychiatric disorders.

Taken together, these findings show that hyperinsulinemia may have a role in the onset of schizophrenia. This has important implications, as elevated insulin levels can have deleterious effects on brain function.³ In addition, this suggests the possibility

CACNA1C (rs1006737) is associated with schizophrenia

Molecular Psychiatry (2010) 15, 119–121; doi:10.1038/mp.2009.89

In a large collaborative study combining three separate whole-genome association studies, the CACNA1C gene (rs1006737) was recently found to display a genome-wide significant association with bipolar disorder (BPD). Here, we report for the first time the
Rule-outs
Considering bipolar disorder

- Risk factors: Earlier onset (<18), family history of bipolar disorder, greater episode frequency
- Irritability, ‘atypical symptoms’ (increased appetite and sleep), moodiness do not necessarily indicate bipolar disorder!
- Treatment-resistant depression does not necessarily indicate bipolar disorder!
- No element of history – other than a manic/hypomanic episode – makes the diagnosis!
- Screen in all depressed patients before initiating treatment.
Screening suggestion: CIDI 3.0

• Some people have periods lasting several days when they feel much more excited and full of energy than usual. Their minds go too fast. They talk a lot. They are very restless or unable to sit still and they sometimes do things that are unusual for them, such as driving too fast or spending too much money. Have you ever had a period like this lasting several days or longer?

• Have you ever had a period lasting several days or longer when most of the time you were so irritable or grouchy that you either started arguments, shouted at people, or hit people?

• www.cqaimh.org/pdf/tool_cidi.pdf
CIDI symptom questions

• Arguments/shouting/hitting?
• Restless/pacing?
• Unusual/embarrassing behavior?
• Taking on too much work?
• Constantly changing plans/activities?
• Hard to focus?
• Thoughts jumping or racing?
• Sleeping less than usual, or less tired?
• Spending too much?
When to pursue general medical workup

• Routine imaging, blood tests not indicated.
• But - in general, anything *unusual* about presentation should prompt a focused workup.

• Examples:
  – Individual symptoms out of proportion to severity
    • cognitive impairment, fatigue
  – Confusion
  – Motor/sensory signs
    • falls, weakness, paresthesias
  – General medical signs (hypothyroid, anemia, …)
Phenocopies: hypothyroid

- Risk of MDD diagnosis if TSH>10:
  - OR ~8.7
- But screening with TSH low yield:
  - inpatients with MDD/anergia
    - 11/250 (4%) hypothyroid
  - patients 60+ with MDD/dysthymia:
    - 5/883 (<1%) have TSH>10
  - patients 18-65 with MDD:
    - 0/200 (0%) have TSH>10

- Better to test in treatment-resistant depression?
  - Prevalence of hypothyroid up to 22%

First line?

- Mild-moderate: med OR psychotherapy
- Moderate-severe: med +/- psychotherapy
- ECT: catatonic/psychotic, or need for urgent response, or preferred by patient

APA Guidelines for Treatment of MDD, 2010
Choice of initial medication

- Effectiveness generally comparable between and within classes.
- Choose based on prior response, adverse effects, PK, patient preference.
- “Has anyone in your family been on antidepressants? What about your friends?”
- In 2012, nearly always always SSRI.

APA Guidelines for Treatment of MDD, 2010
Antidepressant differences are modest... but sertraline and escitalopram look best overall

Figure 4: Ranking for efficacy (solid line) and acceptability (dotted line)

Ranking indicates the probability to be the best treatment, the second best, the third best, and so on, among the 12 antidepressants.
# On the menu

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Daily Dose (mg)</th>
<th>1/2 life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>20</td>
<td>~7d</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>50-200</td>
<td>26 hrs</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil</td>
<td>20</td>
<td>21 hrs</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>20-40</td>
<td>35 hrs</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>10–40</td>
<td>30 hrs</td>
</tr>
<tr>
<td>Venlafaxine^</td>
<td>Effexor</td>
<td>75-300</td>
<td>11 hrs</td>
</tr>
<tr>
<td>Duloxetine^</td>
<td>Cymbalta</td>
<td>30-120</td>
<td>12 hrs</td>
</tr>
<tr>
<td>Bupropion*</td>
<td>Wellbutrin</td>
<td>75-400</td>
<td>20 hrs</td>
</tr>
<tr>
<td>Mirtazapine#</td>
<td>Remeron</td>
<td>15-45</td>
<td>26-37 hrs</td>
</tr>
</tbody>
</table>

^ SNRI, * NERI, # incr NE release
# Points to remember

<table>
<thead>
<tr>
<th>Drug</th>
<th>Entirely subjective, probably biased speaker opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Still works! Long half-life good for poor adherence?</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Expect GI adverse effects</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Caution re withdrawal symptoms, sedation</td>
</tr>
<tr>
<td>Citalopram</td>
<td>May be mildly sedating (like paroxetine); QTc</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Less sedation; no difference in efficacy, sexual AE!</td>
</tr>
<tr>
<td>Venlafaxine^</td>
<td>NE effects only at 150mg+</td>
</tr>
<tr>
<td>Duloxetine^</td>
<td>Take with food, divide dose if nausea</td>
</tr>
<tr>
<td>Bupropion*</td>
<td>Better if sexual AE – contraindicated if seizure risk</td>
</tr>
<tr>
<td>Mirtazapine#</td>
<td>Better if sexual AE – beware sedation/appetite</td>
</tr>
</tbody>
</table>

^ SNRI, * NERI, # incr NE release
“Why pay less???”

- **Desvenlafaxine (Pristiq):**
  - Active metabolite of venlafaxine; SNRI
  - No evidence of superiority
  - Possible benefit (vs venlafaxine) only in 2D6 poor metabolizers (J Clin Psych 2010)

- **Vilazodone (Viibryd):**
  - SSRI+ 5HT1A partial agonist
  - No evidence of superiority
    - In sexual side effects OR time to onset (J Clin Psych 2011)

- **Trazodone XR (Oleptro):**
  - SSRI and 5HT2A antagonist
  - No evidence of superiority
But antidepressants don’t beat placebo… right?

• Tempest in a teapot:
  – Kirsch et al PLOS Medicine 2008: meta-analysis shows no clinically significant benefit versus placebo, except in more severe depression
  – Fountoulakis Int J Neuropsychopharm 2011: Kirsch et al made mathematical errors, selectively reported results
    • Both venlafaxine and paroxetine exceed ‘clinical significance’ threshold.
  – Vohringer Clin Ther 2011:
    • “Relative antidepressant versus placebo benefit increased linearly from 5% in mild depression to 12% in moderate depression to 16% in severe depression”
But antidepressants don’t beat placebo… right?

- At least in US, no FDA-approved placebo!
Alternative and Natural Remedies: Exercise

- “Exercise seems to improve depressive symptoms in people with a diagnosis of depression, but when only methodologically robust trials are included, the effect sizes are only moderate and not statistically significant.” (Cochrane Review, 7/09)

- Tips:
  - 1. Beware the ‘motivation trap’: patients with amotivation may have difficulty implementing an exercise plan!
  - 2. If exercise is preferred as an initial intervention for mild depression, need to plan follow-up within 8 weeks - not 6 months!
  - 3. Avoid late-day exercise which may interfere with sleep
  - 4. Consider monitoring tools (pedometer, eg)
Alternative and Natural Remedies: Complementary medicines

• APA guidelines support St. John’s Wort and SAM-e in *mild* depression

• SAM-e
  – Multiple small studies showing benefit, incl one positive augmentation
    • (meta-analysis: Bressa Acta Neurol Scand 1994)
    • Now one positive RCT (AJP 2010)
  – start 200-400 bid, go up to 800 bid
  – AE: nausea, insomnia, ‘activation’ – dose before 4pm!

• St. John’s Wort (Hypericum)
  – Cochrane 2005: “Current evidence regarding hypericum extracts is inconsistent and confusing.” – but most studies find benefit > placebo.
  – Preparations and dosages vary
  – AE: similar to SSRI
  – Beware CYP450 interactions with SJW!

• Acupuncture
  – Very modest evidence – may be most useful with comorbid pain
Alternative and Natural Remedies: Light box therapy

“For patients suffering from non-seasonal depression, bright light therapy offers modest though promising antidepressive efficacy” (Cochrane 2004)

- Need “10,000 lux” (intensity) – not broad spectrum unless you are growing plants.
- 30-45’, qam, sit close to the box (2-3 feet) but do not look directly at it!
- For seasonal depression, often start Sept/Oct and d/c ~Feb/March
- Beware late-day use which may disrupt sleep
- Sources: google ‘light box’
Setting expectations

“You may start to notice some improvement in the first two weeks – but often people continue to feel better over the first two months…”

Optimal trial is 8-12 weeks!
STAR*D Level 1: Of Ultimate Remitters, 1/2 Remitted after Week 6

52.9%
n=2,876
Remission = QIDS-SR$_{16}$ ≤ 5

Measure symptoms

• Use a waiting-room self-report form such as the QIDS-16 ([www.ids-qids.org](http://www.ids-qids.org))
• Takes 5 minutes!
• Aim for remission (QIDS≤5)

• PHQ-9 can also be used but is probably less sensitive to change…
Managing side effects

• Some follow-up within 1-2 weeks

• Likely to cause non-adherence: weight gain, sexual side effects

• Dangerous: suicidality

• Longer-term: bleeding, weight gain
Some initial side effects get better

Prevalence of SD: Subpopulation of Patients Without Other Probable Causes of SD

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>% of Patients With SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIT</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>VEN XR</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>SER</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>PAR</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>798</td>
<td></td>
</tr>
<tr>
<td>FLU</td>
<td>245</td>
<td></td>
</tr>
<tr>
<td>BUP SR</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

SD defined as at or below threshold total CSFQ score; Data included for antidepressant groups with CI < 30

Sexual Side Effects of SSRI’s Are Common and (Sometimes) Treatable

- Erectile dysfunction & decreased libido more difficult to treat
  - bupropion 150-300mg
  - methylphenidate 10 - 20 mg/d
  - sildenafil or equivalent
  - maca root
Up to 1 in 5 may have ‘significant’ (≥7%) weight gain.

Weight Gain is a Common Long-Term Side-Effect of Current Antidepressant Therapies.
What about the black box warning???

- “Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.
- “Anyone considering the use of [Drug Name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.
- “Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.
- “Families and caregivers should be advised of the need for close observation and communication with the prescriber.”

US FDA package insert text – all antidepressants
High vs low/moderate affinity antidepressants: OR for primary outcomes/negative controls

Primary Outcomes
- Gastrointestinal hemorrhage
- Myocardial infarction
- All strokes
- Ischemic stroke
- Hemorrhagic stroke

Negative Controls
- Acute liver failure
- Acute renal failure
- Asthma
- Breast cancer
- Hip fractures

OR with Confidence Limits

N~37k
Castro BMJ Open 2012; see also Coupland BMJ 2011, Smoller AIM 2010
Citalopram and QTc prolongation

- FDA 8/2011: “Citalopram should no longer be prescribed at doses greater than 40 mg per day.” – and 20mg in age 60+ or poor hepatic function.

- When in doubt, check an EKG
- Document patient awareness of warning
- Avoid in CHF, h/o bradyarrhythmia, hypokalemia
- Avoid other QTc-prolonging drugs – most antipsychotics, methadone
- Avoid strong CYP2C19 inhibitors (eg, protease inhib)
- Useful: qtdrugs.org; Roden NEJM 2004
Figure 1. Adjusted hazard ratios (HR; adjusted for age, sex, race, state, nursing home residence, an ever-past bipolar disorder diagnosis, and an ever-past angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker prescription) for sudden cardiac death and ventricular arrhythmia associated with antidepressant exposure, using paroxetine as the reference (ref)
Talk therapy
Psychosocial Therapies: a prescriber’s guide

- Trends to watch:
  - Group interventions – more efficient, similar efficacy
  - Brief interventions – 12 weeks or less
  - Delivery by trained non-PhD
    - Less stigma by labeling as ‘coaching’ or ‘stress management class’
  - Real CBT versus ‘I bought the manual’

- Consultation model: initial evaluator may not be treater, and should give input regarding appropriate type of therapy
- Appropriate to ask about, and collaborate on, setting treatment goals
  - As with meds, talk therapy has risks and benefits
When the first treatment fails
The Overall Remission Rate in Level 1 of STAR*D was 32.9% (N=943/2876), based on the QIDS-SR

Approach to treatment-resistant MDD

• 1. Adherence okay?

• 2. Correct diagnosis?
  – Anxiety, substance use disorder
  – Bipolar disorder (don’t panic!)

• 3. Comorbidity addressed?

• 4. Consultation needed?

APA Guidelines for Treatment of MDD, 2010
Rules of thumb

• Titrate to therapeutic dose by 2 weeks.
• At/after 4 weeks
  – If improving, continue to follow
  – If not improving and tolerating, increase dose
  – If not improving and not tolerating, augment or switch
• Adequate trial is 8-12 weeks
• Measure symptoms (QIDS-SR, PHQ-9)
At 8-12 wk, switch or augment?

- Minimal response or poorly tolerated: **switch** (within-class, then across-class)

- Partial response: **augment/combine**
  - CBT
  - Antidepressant from another class (bupropion, e.g.)
  - Second-generation antipsychotic
  - Lithium or thyroid hormone

APA Guidelines for Treatment of MDD, 2010
STAR*D, in a nutshell

• Switching:
  – Venlafaxine=sertraline=bupropion
  – Mirtazapine=nortriptyline

• Augmenting:
  – Bupropion=buspirone
  – Lithium=T3

Negative spin: it doesn’t matter what you do.
Positive spin: it’s about time not treatment choice.

Rush NEJM 2006; Fava AJP 2006; Trivedi NEJM 2006
Augmentation

• FDA-approved, most data, but safety/cost concerns:
  – Aripiprazole (Abilify)
    • Start 2-5mg, aim for 5-10mg
    • Beware activation/akathisia, sedation, weight gain, metabolic symptoms
  – Quetiapine (Seroquel)
    • Start 50mg, aim for 100-150mg
    • Beware sedation, weight gain, metabolic symptoms
  – Olanzapine (Zyprexa) – really approved for TRD, in combination with fluoxetine
    • Start 2.5-5mg, aim for 2.5-10mg
    • Beware sedation, weight gain, metabolic symptoms
Augmentation (cont’d)

Commonly used without FDA-approval:
- Bupropion (100mg-400mg qam/bid)
- Buspirone (5bid up to 20tid)
- Pramipexole (0.25mg up to 3mg qhs)
- Modafinil (200-400mg qam/bid)
- Stimulants (eg, dexedrine 5qam -> 10bid or more)
- Deplin (methylfolate) (7.5bid)

- Older strategies:
  - Lithium (low-dose), synthroid (25-50mcg), tricyclic antidepressant

- And don’t forget CBT!
Simple Discovery

Leads to Great New Taste Sensation in Cereal

When we tried sugar coating our big, crisp flakes of corn, they tasted fine. But not until we treated in the secret sugar frosting did we really get excited. Out of our ovens popped a sparkling new flavor. Ever tried the new cereal with the toasted-in sugar flavor? Quite a find...in sparkling go-ahead energy, too.

Kellogg's Sugar Frosted Flakes
What about newer agents?

- Atypical antipsychotics: olanzapine, quetiapine, aripiprazole
- Others may work but are earlier or later in development cycle
- Challenges: metabolic syndrome/obesity
‘Weight neutral’??

12-week weight change in treatment-naïve children and adolescents

Correll JAMA 2009
Modafinil Augmentation in SSRI Partial Responders with Persistent Fatigue and Sleepiness

*\( p = 0.02 \) for difference in overall distribution of scores between modafinil and placebo groups.

Double-Blind Study of SAMe Augmentation in SSRI-Resistant Depressed Patients

FIGURE 2. HAM-D Response and Remission Rates Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo

- Placebo + Antidepressant (N=34)
- SAMe + Antidepressant (N=39)

**Response Rates**
- Placebo: 10
- SAMe: 50

**Remission Rates**
- Placebo: 15
- SAMe: 45

*a* Data depict last observation carried forward (LOCF) for all patients randomly assigned.

*b* Significant difference between groups (p<0.05, Fisher’s exact test).

Papakostas G et al; Am J Psychiatry 2010; 167:942–948
Open-Label Study of Riluzole Augmentation in TRD

Ketamine? Not yet.

• IV Ketamine studies (with caveats) suggest rapid antidepressant efficacy – but
  – Efficacy not sustained
  – IV administration requires monitoring
  – Safety concerns may constrain widespread use

• *Probably most important as a probe for developing novel therapeutics targeting NMDAR (glutamate)*

Diazgranados Arch Gen Psych 2010
ECT works.

- Most efficacious form of antidepressant treatment available.

- Indicated for treatment-resistant depression, psychotic depression, and depression in the critically ill who may not be able to tolerate the adverse effects and 2-6 week latency to response of antidepressant drugs – “or whenever preferred by patient”
Other somatic therapies

- Transcranial magnetic stimulation (TMS)
- Vagus nerve stimulation (VNS)
- Deep brain stimulation (DBS) – still experimental
Remission/long-term treatment
Not out of the woods...

- Depression is frequently recurrent.
- After a first episode, may taper antidepressant at ~ 4-9 months.
- After subsequent episode, or if initial episode chronic or difficult to treat, long-term antidepressant use should be considered.

APA Guidelines for Treatment of MDD, 2010
TRD = greater recurrence risk

- More trials to respond -> more risk

N~2,248 exiting to follow-up in STAR*D; Rush AJP 2006
Prevalence of Cognitive Symptoms in Responders to Antidepressant Treatment (n=117)

Key questions

• How do I screen?
• When is further workup indicated?
• What is first line treatment?
• What are reasonable next steps?
  – “and what’s with those TV commercials???”
• “But I just prescribe exercise!”
• What about other complementary/alternative options?
• Am I missing bipolar disorder?
Management of Major Depressive Disorder

Roy Perlis, MD MSc
Center for Experimental Drugs and Diagnostics (CEDD)
Department of Psychiatry
Center for Human Genetic Research
Massachusetts General Hospital

rperlis@partners.org