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University of Washington

AIMS CENTER
Advancing Integrated Mental Health Solutions

Building on 25 years of Research and Practice in Integrated Mental Health Care

Medication Therapy for Depression and Anxiety

Jürgen Unützer
Collaborative Team Approach

- PCP
- Patient
- Care Manager
- Consulting Psychiatrist
- Other Behavioral Health Clinicians
- Substance Treatment, Vocational Rehabilitation, Other Community Resources

New Roles
- Core Program
- Additional Clinic Resources
- Outside Resources

Only a Minority of Patients Receive Effective Treatment

Almost 30 million Americans receive a prescription for an antidepressant in any given year

- ~ 20 - 30 % Drop out of treatment too early
- ~ 25 - 50 % Stay on ineffective treatments for too long
Remember:
Most Patients Need Treatment Adjustments

Over 30 – 50% of patients will have a complete response to initial treatment

50 – 70% will require at least one change in treatment to get better

Using Antidepressants

Key principles
– Use antidepressants, not minor tranquilizers / benzodiazepine for depression and most anxiety disorders
– Use adequate doses for an adequate amount of time
– Start slow and work with side effects but titrate to an effective dose as needed
– Change medication if not effective
  • Usually after 8 – 10 weeks
FDA-Approved Antidepressants

Serotonin Reuptake Inhibitors (SSRIs)
- fluoxetine (Prozac), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), sertraline (Zoloft), fluvoxamine (Luvox)

Newer Antidepressants (atypical)
- bupropion SR (Wellbutrin), mirtazapine (Remeron), venlafaxine XR (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta)

Tricyclics (TCAs)
- secondary amines: nortriptyline, desipramine, amitriptyline
- tertiary amines: imipramine, doxepin, amitriptyline
  
  Not recommended for older adults
# Serotonin Reuptake Inhibitors (SSRIs)

*Common side effects in all SSRIs (>10 %): GI distress (nausea, diarrhea), insomnia, restlessness, agitation, fine tremor, headache, dizziness, sexual dysfunction.*

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Unit doses avail.*</th>
<th>Therapeutic dose*</th>
<th>Usual dose*</th>
<th>Starting dose*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>10, 20</td>
<td>10-60</td>
<td>20</td>
<td>10 daily</td>
<td>Long half-life</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50, 100</td>
<td>25-200</td>
<td>50-100</td>
<td>25 daily</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>20, 40</td>
<td>10-40</td>
<td>20</td>
<td>10 daily</td>
<td>Few drug interactions</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5, 10, 20</td>
<td>10-20</td>
<td>10</td>
<td>10 daily</td>
<td>Few drug interactions</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10, 20, 30, 40</td>
<td>10-50</td>
<td>20-30</td>
<td>10 daily</td>
<td>Dry mouth, constipation</td>
</tr>
</tbody>
</table>

# New Antidepressants: SNRIs

*SNRI side effects: GI distress (NAUSEA, diarrhea), insomnia, restlessness, agitation, fine tremor, headache, dizziness, constipation, decreased appetite, sexual dysfunction.*

*Small risk of elevation of blood pressure at higher doses => check BP.*

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Unit doses avail.*</th>
<th>Therapeutic dose*</th>
<th>Usual dose*</th>
<th>Starting dose*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>25, 37.5, 50, 75, 100</td>
<td>12.5-150 bid</td>
<td>25-100 bid</td>
<td>25 daily</td>
<td>Once daily dosing with XR preparation.</td>
</tr>
<tr>
<td></td>
<td>XR 37.5, XR 75, XR 150</td>
<td>37.5-225 daily (XR)</td>
<td>75-225 daily (XR)</td>
<td>37.5 daily (XR)</td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50, 100</td>
<td>50 – 100</td>
<td>50 daily</td>
<td>50 daily</td>
<td>Active metabolite of venlafaxine; similar side effect profile.</td>
</tr>
</tbody>
</table>
## New Antidepressants: SNRIs – II

*SNRI side effects: GI distress (NAUSEA, diarrhea), insomnia, restlessness, agitation, fine tremor, headache, dizziness, constipation, decreased appetite, sexual dysfunction.*

Small risk of elevation of blood pressure at higher doses => check BP.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Unit doses avail.*</th>
<th>Therapeutic dose*</th>
<th>Usual dose*</th>
<th>Starting dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>20, 30, 60</td>
<td>40 – 60 daily</td>
<td>40 – 60 daily</td>
<td>30 daily</td>
</tr>
</tbody>
</table>

**Comments**

Nausea, dry mouth, constipation, decreased appetite, fatigue, sweating, sexual dysfunction.

Enteric coated. *DO NOT break tablets!*

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## Mirtazapine

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Unit doses avail.*</th>
<th>Therapeutic dose*</th>
<th>Usual dose*</th>
<th>Starting dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>15, 30</td>
<td>15-45 qhs</td>
<td>15-30 qhs</td>
<td>7.5 -15 qhs</td>
</tr>
</tbody>
</table>

**Comments**

Sedation, weight gain.

Minimal sexual side effects.

May help with anxiety / nausea.

*mg
### Bupropion

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Unit doses avail.*</th>
<th>Therapeutic dose*</th>
<th>Usual dose*</th>
<th>Starting dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>75,100</td>
<td>75-150 tid</td>
<td>75-150 tid</td>
<td>75 daily</td>
</tr>
<tr>
<td></td>
<td>SR 100, 150</td>
<td>100-200 bid (SR)</td>
<td>100-200 bid (SR)</td>
<td>100 daily (SR)</td>
</tr>
<tr>
<td></td>
<td>XL 150, 300</td>
<td>150-450 daily (XL)</td>
<td>150-300 daily (XL)</td>
<td>150 daily (XL)</td>
</tr>
</tbody>
</table>

**Comments**
- TID dosing with regular preparation.
- BID dosing with SR. Daily dosing with XL.
- Insomnia, agitation, tremor.
- Anorexia; no weight gain.
- Risk of seizures at high doses.
- Minimal sexual side effects.
- Perhaps less mania induction in bipolars
- Not good for anxiety.

*mg

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### Secondary Amine Tricyclics (TCAs)

*Common side effects in all TCAs (>10%): arrhythmias (particularly with pre-existing conduction defects), dry mouth, constipation, blurry vision, orthostatic hypotension, and weight gain.*

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Unit doses avail.*</th>
<th>Therapeutic dose*</th>
<th>Usual dose*</th>
<th>Starting dose*</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline</td>
<td>10, 25, 50, 75</td>
<td>40-150</td>
<td>50-100</td>
<td>10 qhs</td>
<td>Weakness/fatigue</td>
</tr>
<tr>
<td>Desipramine</td>
<td>10, 25, 50, 75, 100, 150</td>
<td>75-200</td>
<td>100-200</td>
<td>25 daily</td>
<td>Tachycardia, insomnia, agitation</td>
</tr>
</tbody>
</table>

*mg
Choosing Antidepressants

Prior treatment history in patient/family members
Patient preferences
Expertise of prescribing provider
Side effect profile
Safety in overdose
   – 10 days of a TCA can be a lethal overdose
Availability and costs
Drug-drug interactions

When and How to Stop Antidepressants?

Treat all adults for 6-9 months after initial response
Treat those at high risk for relapse for 2 years or longer. Some may need lifetime treatment
Maintenance treatment should be at full dose
Make a relapse prevention plan
Taper antidepressants slowly to avoid discontinuation syndrome
### Problems Early in Treatment

1. **Nonadherence**
2. **Medical and psychiatric comorbidity**
3. **Side effects**
4. **Unmasking bipolar disorder**
5. **Activation and suicidal ideation**
6. **Incomplete response**

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General Office Strategies for Optimizing Adherence

Provide rationale for use
Careful attention to side-effects (see below)
Counter demoralization
Address fear of dependence and loss of control
Enlist family/spousal support
Address concerns in relation to patient’s or significant other’s prior experience with medication
Increase contact with brief phone check-ins
Specific instructions (take regardless of symptom change, don’t stop on own)
Use symptom scale (e.g., PHQ-9)

Is Patient at Maximum Therapeutic Dosage?*

- Fluoxetine 60mg
- Paroxetine 60mg
- Escitalopram 20mg
- Citalopram 60mg
- Sertraline 200mg
- Venlafaxine 300mg
- Desvenlafaxine 100mg
- Duloxetine 60mg
- Bupropion SR 450mg
- Mirtazapine 60mg
- Nortriptyline 150mg (check serum level)
- Despramine 300mg (check serum level)

*Consider titrating to these doses unless patient does not tolerate them ‘maximum doses’ due to side effects.
Managing Side Effects

Consult with pharmacist / team psychiatrist
  – Are side effects ‘physical’ or ‘psychological’?

Short term strategies
  – Wait and support (e.g., GI side effects of SSRIs)
  – Adjust medication timing (e.g., take sedating meds at bedtime)
  – Consider temporary dose reduction
  – Treat side effects (if drug effective)

Change to a different antidepressant
Change to or add PST-PC
Common Side Effects

Short term:
- GI upset / nausea
- Jitteriness / restlessness / insomnia
- Sedation / fatigue

Long term:
- Sexual dysfunction (up to 33%)
- Weight gain (5 to 10%)

Orgasmic Dysfunction

25 – 33% of SSRI-treated patients

Change to
- Bupropion
- Mirtazapine

Augment
- Bupropion SR 100mg PO BID
- Buspirone 15mg PO BID to 30mg PO BID
Weight Gain

5 to 10% of SSRI treated patients

Rx – Bupropion, Fluoxetine

Drug-Drug Interactions

Antidepressants are metabolized by the P450 isoenzyme system in the liver. They can
– change blood levels of other drugs that are metabolized by the same hepatic enzymes
– displace other protein-bound drugs

Rule of thumb: if a patient is on a drug with a narrow therapeutic window (e.g., digoxin, warfarin, theophylline, antiarrhythmics, lithium, TCAs, anticonvulsants), check a serum level of that drug when a steady state of the antidepressant is reached or if there are side effects

Consult pharmacist
Good Reasons to Stop a Medication

Intolerable side effects

Dangerous interactions with necessary medications

The medication was not indicated to start with (e.g., bipolar depression)

Medication has been at maximum therapeutic dose without improvement for 4-8 weeks

What if Patients Don’t Improve?

Is the patient adhering to treatment?

Is the dose high enough?
  – See max dose guidelines

Is the diagnosis correct?
  – ? Bipolar depression
  – ? Medical conditions (hypothyroidism, sleep apnea, pain)
  – ? Meds: steroids, interferon, hormones
  – ? Withdrawal: stimulants, anxiolytics

Are there untreated comorbid conditions / life stressors?
Bupropion-SR, Sertraline or Venlafaxine-XR after Failure of SSRIs for Depression

Rush et al., *NEJM*, 2006

About one in four patients had a response after switching to a new antidepressant with no differential effect

Medication Augmentation after the Failure of SSRIs for Depression

Trivedi et al., *NEJM*, 2006

No differences in response rates, but bupropion was associated with greater reduction in depressive symptoms and lower dropout from side-effects than buspirone
CBT in STAR-D

Switch from citalopram to CBT or augmentation of citalopram with CBT
– Only 26% accepted CBT as an option at ‘level 2’

Remission over 12 weeks not significantly different from medication comparators
– 25 and 23%

CBT took longer but had fewer side effects

STAR-D Remission Rates Based on Number of TREATMENT STEPS

<table>
<thead>
<tr>
<th>Step</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Step</td>
<td>36.8%</td>
</tr>
<tr>
<td>Second Step</td>
<td>30.6%</td>
</tr>
<tr>
<td>Third Step</td>
<td>13.7%</td>
</tr>
<tr>
<td>Fourth Step</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

Bottom line: 1/3 respond with initial treatment but almost all patients respond eventually

Caveat: those requiring more Rx steps had higher relapse rates during naturalistic follow-up
Antidepressant Summary

There are over 30 FDA-approved antidepressants
- Each is effective in ~ 40 – 50% of patients
- It may take several trials until an effective medication is identified
- Patients need support during this time (work with care manager)

If medications are not effective after 8 – 10 weeks at a therapeutic dose
- Is patient taking medication as prescribed?
- Consider substance abuse, bipolar disorder, anxiety disorders, cognitive impairment. Ask every patient about suicidal ideation
- Consult with team psychiatrist and change treatment (medications, other somatic treatments, psychotherapy)

Overview of Medication Therapy for PTSD & Anxiety
Psychopharmacology for PTSD & Anxiety Disorders

More similarities than differences among common anxiety disorders
- PD, GAD, SAD, PTSD

SSRIs and SNRIs are equally efficacious for anxiety and depression

Medications targeting arousal symptoms (e.g., insomnia) important

Why Antidepressants for PTSD & Anxiety?

Most antidepressants are efficacious for PTSD / anxiety disorders

Comorbid depression common

No risk of abuse
Anxiety Psychopharmacology
Initial Medication Choice

No prior history: start with SSRI

No evidence that one SSRI is better than another

If patient has had a definite prior response to a non-SSRI and patient prefers this, may use SNRI, mirtazapine, or TCA

Be careful about assuming prior medication trials were ineffective—must confirm that optimal dose (top doses) and durations (12 week minimum) were used

Titration of Medication Treatment

START LOW, GO SLOW to avoid excessive activation and side effects – but titrate to therapeutic dose over 4-6 week period

Titrate partial responders after 4-6 weeks to higher doses if tolerated: try to get to maximum doses AND durations
Evidence-based Medication for PTSD & Anxiety

SSRI (fluoxetine/Prozac, sertraline/Zoloft, paroxetine/Paxil, citalopram/Celexa)

SNRI (venlafaxine/Effexor, duloxetine/Cymbalta)

Prazosin & trazadone/Desyrel targeting arousal symptoms (e.g., sleep)

Care Manager Role in Supporting Medication Therapy
Supporting Medication Therapy

Become familiar with commonly used antidepressant and other psychotropic medications and medication doses

Provide basic patient education about medications commonly prescribed in primary care

Support medication adherence

Know when treatment is ‘not working’ and alert the rest of the team to facilitate a change

Supporting Medication Therapy

Help patients and providers identify…

– Potentially inadequate doses
– Ineffective treatment (e.g., persistent symptoms after adequate duration of medication trial)
– Side effects

Facilitate patient-provider (e.g., PCP) communication about medications

Consult with PCP and team psychiatrist about medication questions
Patient Education
About Antidepressants

Key messages
– How do these medications work?
  • By restoring a chemical imbalance in the brain
– There are many options (over 30 available medications)

Anticipate
– Patient concerns about medications
– Side effects (these can be managed)
– Problems with adherence

Reinforce
– Need for continuation or maintenance treatment to prevent relapse even after the patient feels better

Antidepressant Adherence

Key messages:
– Take medication daily
– Wait 2-4 weeks for effect
– Side effects can occur, but often resolve in 1-2 weeks
– Keep taking medication even if better
– Check with MD before stopping
– Not addicting

Lin EH., Med Care 1995;33:67
Collaborative Team Approach

- PCP
- Patient
- Care Manager
- Consulting Psychiatrist
- Other Behavioral Health Clinicians
- Substance Treatment, Vocational Rehabilitation, Other Community Resources

New Roles
- Core Program
- Additional Clinic Resources
- Outside Resources

Questions?

For questions about specific treatments or patients, contact your team psychiatrist.