Clinical Updates
Management of Anxiety Disorders
John So - Psychiatrist

foreword

- Six Persimmons 《六柿圖》
- Muqi Fachang 牧谿法常
- after Zen meditation
  - mindfulness
  - other trends of psychotherapy
- other modalities of treatments
- by evidence or impression?

general

- anxiety disorders
- normal emotion → disorders
  - becoming disabling
  - reducing quality of life
- characteristics
  - different types
  - prone to have co-morbidities
  - prone to be chronic

- drugs
  - benzodiazepine
  - antidepressant (SSRI SNRI)
  - others
    - other antidepressants
    - other agents

BZ

- benzodiazepines
  - rapid symptomatic relief
  - efficacy
    - pooled analysis showed less risk of treatment discontinuation due to lack of efficacy as compared to placebo (Martin J. et al, 2007)

- benzodiazepines
  - rapid symptomatic relief
  - efficacy
  - recommendation
    - only for severe, disabling or extremely distressing anxiety
    - dependence, withdrawal risks
      - lowest effective dose
      - shortest period (maximum 4/52)
      - caution with substance misuse
• benzodiazepines
  • rapid symptomatic relief
  • real world...
  • over-prescription
    • Harvard / Brown Anxiety Research Project (HARP)
      • naturalistic, longitudinal, multisite study of adults with anxiety disorders (Benitez CI et al., 2008; Vaste RG et al., 2010)
      • psychiatric setting

• benzodiazepines
  • over-prescription
    • Harvard / Brown Anxiety Research Project (HARP)
      • Clonazepam 1.6mg
      • Alprazolam 2.0mg
      • Lorazepam 2.8mg
      • Diazepam 13.0mg

• benzodiazepines
  • rapid symptomatic relief
  • real world...
  • over-prescription
    • “should not be denied”
      • “a very small number of patients with severely disabling anxiety may benefit from long-term... benzodiazepine” (12th Maudsley Guidelines, 2015)
<table>
<thead>
<tr>
<th>Generic name</th>
<th>use</th>
<th>Classical 5-HTR</th>
<th>Non classical 5-HTR</th>
<th>Positive modulator</th>
<th>Antagonist</th>
<th>Ki (nM)</th>
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</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>clinical</td>
<td>□</td>
<td>α1/α2/α5</td>
<td>all</td>
<td>15-17</td>
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<tr>
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<td>□</td>
<td>α1/α2/α5</td>
<td>α3</td>
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<td></td>
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<tr>
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<td>□</td>
<td>all</td>
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<tr>
<td>Flavoxetin</td>
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<td>□</td>
<td>all</td>
<td>0.5-1.5</td>
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<td>Zolpidem</td>
<td>clinical</td>
<td>□</td>
<td>all</td>
<td>200-600</td>
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<tr>
<td>Buspirone, L-838,417</td>
<td>experimental</td>
<td>□</td>
<td>α2/α3</td>
<td>α5</td>
<td>0.3</td>
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<td>□</td>
<td>α2/α3</td>
<td>α5</td>
<td>0.2-0.5</td>
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<tr>
<td>Imipramin</td>
<td>experimental</td>
<td>□</td>
<td>α2/α3</td>
<td>α5</td>
<td>N/A</td>
<td></td>
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</table>

(Tan KR et al., 2011)

**SSRI / SNRI**

- SSRI antidepressant
- Efficacious first-line drug
- SNRI antidepressant
- Venlafaxine and duloxetine
- Short and long term for GAD
- Venlafaxine
- Acute treatment and relapse prevention in panic disorder

(Baldwin D et al., 2014)

**SSRI / SNRI x GAD**

- SSRI / SNRI x GAD
- Dosing
  - 1 / 2 normal starting dose
  - Some have initial worsening of anxiety (Scott A et al., 2001)

(Baldwin D et al., 2014)

**SSRI / SNRI x GAD**

- SSRI / SNRI x GAD
- Dosing
  - 1 / 2 normal starting dose
  - Titration upwards
  - Normal dosage as tolerated
  - Predictors: severity and duration of symptoms, (neuroimaging?)
  - Response within 6 weeks, continues to increase over time (Baldinger K, 2004, Baldwin D et al., 2006, 2011)
SSRI / SNRI x GAD

- SSRI / SNRI x GAD
- dosing
  - 1/2 normal starting dose
  - titration upwards
  - at least 1 year treatment
  - longer continuation treatment (Baldwin DS et al, 2011)

- may prevent depression; drug tx NOT associated with depression (Goodwin RD & Gorman JM, 2002)

- drug choice (Baldwin D et al, 2011b)
  - Fluoxetine
    - probably most effective
  - Sertraline
    - probably best tolerated

Rank Response
1 Fluoxetine
2 Lorazepam Escitalopram Pregabalin
3 Duloxetine Venlafaxine Fluoxetine
4 Sertraline Paroxetine Paroxetine
5 Paroxetine Sertraline Tiagabine
6 Pregabalin Duloxetine Venlafaxine
7 Venlafaxine Tiagabine Escitalopram
8 Escitalopram N/A Duloxetine
9 Tiagabine N/A Lorazepam

(Baldwin D et al, 2011b)
Efficacy of drug treatments for GAD: systematic review and meta-analysis.

Systematic review of RCT:
46 randomised controlled trials
27 with sufficient or appropriate data

Primary Bayesian probabilistic mixed treatment meta-analyses allowed pharmacological treatments to be ranked for effectiveness for each outcome measure, given as percentage probability of being the most effective treatment.

(i.e. less withdrawal for adverse events)

SSRI / SNRI x GAD

• SSRI / SNRI x GAD
  • dosing
  • drug choice (Baldwin D et al, 2011b)
    • Fluoxetine
      • probably most effective
    • Sertraline
      • probably best tolerated

SSRI / SNRI x others

• SSRI / SNRI x panic disorder
  • dosing (12th Maudsley Guidelines, 2015)
    • 1 / 2 normal starting dose
    • titration upwards
      • bottom antidepressant range
    • paroxetine may need higher dose
    • response as long as 6 weeks

• unpublished data, sponsorships, publication bias, methodology...
• GAD highly variable, racial disparities...
### SSRI / SNRI x others

**SSRI / SNRI x panic disorder**

- **dosing** *(12th Maudsley Guidelines, 2015)*
  - 1 / 2 normal starting dose
  - titration upwards
  - at least 8 months
  - optimal duration undetermined *(Rickels K & Schweizer E, 1998)*
  - evidence of benefit for at least 3 years *(Choy Y et al, 2007)*

**disorder dosing response** *(week)*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dosing</th>
<th>Response (week)</th>
<th>Minimum (month)</th>
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<tbody>
<tr>
<td>GAD</td>
<td>half starting dose titrate to normal dose</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>half starting dose titrate to normal dose</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>standard dose titration may not be required</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>OCD</td>
<td>higher licensed dose but standard dose may suffice</td>
<td>10 to 12</td>
<td>12</td>
</tr>
<tr>
<td>PTSD</td>
<td>lower starting dose high dose often required</td>
<td>8 to 12</td>
<td>6</td>
</tr>
</tbody>
</table>

*(12th Maudsley Guidelines, 2015)*

- **drug choice**
  - SSRI first line
  - clonazepam augmentation
    - may lead to more rapid response, but not greater overall response *(Pollack HM et al, 2003)*

- **other antidepressants**
  - TCA
    - efficacy
      - efficacious in some anxiety disorders
    - more side effects *(Baldwin DS et al, 2014)*
  - clomipramine augmentation
  - agomelatine
    - melatonergic and serotonergic
      - MT(1), MT(2), 5-HT(2C) receptors
    - efficacy
      - efficacious in GAD, RCT vs placebo, fu 12 weeks and 6 months *(Stein DJ et al, 2008, 2012)*
      - less sexual or withdrawal side effects; liver function monitor *(Baldwin DS et al, 2014)*
Results of AMSP: a Drug Surveillance Program (Friedrich ME et al., 2016)

Arzneimittelsicherheit in der Psychiatrie

• Other antidepressants
  - Mirtazapine (Baldwin DS et al., 2014)
  - Noradrenergic and Specific Serotonergic Antidepressant
  - Efficacy
    - Limited and inconsistent evidence
    - Probably less frequent sexual dysfunction

• Other antidepressants
  - Bupropion (Baldwin DS et al., 2014)
  - Noradrenergic, dopaminergic
  - Efficacy
    - Non-specific anxiolytic effect, pilot study support
    - Concomitant BZs are necessary (Coplan JD et al., 2015)

• Other antidepressants
  - TCA
  - Agomelatine
  - Mirtazapine
  - Bupropion

• Other agents
  - Pregabalin
    - Ca channel α2δ subunit ligand
    - Efficacy
      - Efficacious in GAD (Baldwin DS et al., 2015, Pollack MH, 2009)
      - Initial dose 150mg
      - Comparable onset with BZ: abrupt stop may cause rebound anxiety and seizures (12th Maudsley Guidelines, 2015)
• **other agents**
  - quetiapine
    - atypical antipsychotic
    - efficacy
      - dose from 50 to 150 or 300mg
      - low acceptability and tolerability, generally for non-response cases (Baldwin DS et al, 2011)
  - buspirone
    - azapirone anxiolytic
    - 5-HT1A, 5-HT2A, D2, α1-adrenergic and α2-adrenergic receptors
    - efficacy
      - efficacious in GAD, not superior to BZ, not as acceptable as BZ (Chessick CA et al, 2006)
  - hydroxyzine
    - 1st generation antihistamine
    - efficacy
      - efficacious in GAD, also tolerable, may be as effective as chlordiazepoxide or buspirone (noting study limits) (Guaiana G et al, 2010)
  - flupentixol-melitracen (Wang L et al, 2015)
    - “Deanxit”
    - efficacy
      - chronic somatic diseases associated anxiety symptoms
      - RCT response rates favouring addition to sertraline to lower anxiety for first two weeks
      - potential tardive dyskinesia risk
  - SSRI / SNRI
    - fluoxetine
    - sertraline
  - other antidepressants
    - TCA
    - agomelatine
    - mirtazapine
    - bupropion
  - benzodiazepine
  - other agents
    - pregabalin
    - quetiapine
    - buspirone
    - hydroxyzine
    - flupentixol-melitracen
anxiety disorders

• drug treatments
• noting other modalities
• generally, SSRI first line
• temporarily, BZ coverage
• response around 6 to 12 weeks
• prone chronic and co-morbid

• limits
• evidence issues
• access to data, publication bias, methodology limits
• cultural and biological differences
• side effects and withdrawals
• “guideline” issues

Reference