Pharmacological Treatment of Anxiety Disorders

Christer Allgulander

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Disclosures

Advisor: Pfizer Sweden, PRIMA Barn & Vuxen Psykiatri AB (private health care provider)

Speaker: Eli Lilly, Pfizer, The Police Academy
Objective
To obtain a clinical and research update on the current use of anxiolytics in patients with morbid anxiety.

Outline
Pharmacoepidemiology
GAD, Social Anxiety, Panic Anxiety
Guidelines
Relapse prevention
Anxiety in somatic disease
The elderly
Benzodiazepines
Ethnicity
Adherence
**Total Cost** of Brain Disorders in Europe 2010

Prescriptions in outpatient care in Sweden, 2002

Daily therapeutic doses per 1000 inhabitants

Apoteket, 2003
Antidepressants/anxiolytics in primary care - Piedmont (pop. 1,057,053)

Treatment for Anxiety/Depression in the UK ICD-10 Survey (N=10,108)

The likelihood of treatment increased with symptom severity

Bebbington PE et al. Psychol Med 2000;30:1369-76
GAD treatment guidelines: WFSBP 2008

First line: Pregabalin
SSRIs†
SNRIs

4-6 weeks

Response?

Yes

Continue

Partial

Further 4-6 weeks

No

Change dose or switch

✓ Benzodiazepines (second line due to abuse potential)
  - Treatment-resistant patients with no history of dependence
  - Add-on to SSRIs/SNRIs in first few weeks until onset of efficacy of antidepressant

✓ Tricyclic antidepressants
  - Imipramine effective, but lethal in overdose and tolerability less than first-line

Evidence-based pharmacotherapy in GAD

- Venlafaxine XR
- Escitalopram
- Paroxetine
- Pregabalin
- Sertraline
- Duloxetine
  - Benzodiazepines (short-term, not antidepressant)
  - Buspirone (antiaggressive, not antidepressant)
  - Imipramine (1 RCT)
  - Hydroxyzine (3 RCTs)

Baldwin et al. BAP guideline, J Psychopharmacol 2014;28:403-39
Comorbid GAD and insomnia

Adding eszopiclone to escitalopram treatment for 8 weeks resulted in a more rapid response and higher response rate.

Social Anxiety Disorder
Amygdala Response to Novelty
Inhibited infants grown up

Guideline for treatment

- Patient education (booklet)

- Medications
  - beta-blocking agents (performance anxiety)
  - Paroxetine, escitalopram, fluvoxamine, sertraline
  - Venlafaxine
  - Clonazepam

- CBT, internet, self-help

Behavioural effects of treatment

Patients with generalized anxiety on paroxetine and similar medications improved with regard to harm avoidance, cooperativeness, and self-directedness.
Gittelman-Klein R, Klein DF. Controlled imipramine treatment of school phobia. Arch Gen Psychiatry 1971;25:204-207
Study of 96 new patients with social anxiety disorder

- Advertisements for previously untreated cases in Stockholm
- Paroxetine 20-50 mg vs. placebo for 3 months
- Palm computer (Minidoc®) for LSAS, SDI, BSPS, FONE
Liebowitz Social Anxiety Scale
Total score

Change in LSAS score

* * * p = 0.052; ** p < 0.01; *** p < 0.0001

Paroxetine
Placebo

Sheehan Disability Inventory: Work

** p<0.01
Panic Disorder
How to assess and monitor anxiety symptoms
Implications for Symptom Measurement

## Hamilton Rating Scale for Anxiety

<table>
<thead>
<tr>
<th>Item</th>
<th>Psychic</th>
<th>Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anxious mood</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>2 Tension</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>3 Fears</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>4 Insomnia</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>5 Intellectual (cognitive)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6 Depressed mood</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>7 Somatic (muscular)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>8 Somatic (sensory)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>9 Cardiovascular symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>10 Respiratory symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>11 Gastrointestinal symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>12 Genitourinary symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>13 Autonomic symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>14 Behaviour at interview</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

### HAM-A Scoring
- >25: Severe anxiety
- 19-25: Moderate anxiety
- 8-18: Mild anxiety
HAM-A Effect Size at 6 Months

Anxiolytics approved in Europe

<table>
<thead>
<tr>
<th></th>
<th>Panic disorder</th>
<th>GAD</th>
<th>Social anxiety</th>
<th>OCD</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sertraline</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Citalopram</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Duloxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Relapse prevention study in GAD

Escitalopram responders were randomized to continued escitalopram or placebo for up to 19 months.

Time to relapse

ESC N=186 relapses: 35 (18.8%)
PBO N=187 relapses: 105 (56.1%)
Hazard ratio = 4.04
Work satisfaction and efficacy in GAD (LOCF)

* = P<0.005  
Multiple prescriptions for psychoactive medications; GAD patients in specialized care, Sweden

Number of patients in each category

Anxiety in somatic diseases
Risk of cardiovascular events in stable CHD in the presence and absence of GAD

Martens et al. Arch Gen Psychiatry 2010;67:750-758

Cumulative Risk

Current anxiety

No current anxiety

n=767
P=0.001

Months, No.
Association between symptoms of depression/anxiety and diabetes type 2

- A prospective population-based study in 37,291
  - 10 year follow up using questionnaire-based assessments
  - Anxiety and depression caseness based on the ADI
- Symptoms of depression and anxiety were significant risk factors for the onset of type 2 diabetes
  - No gender differences
  - No underlying factors that mediated the association were identified
  - Independent of established risk factors for diabetes, such as socioeconomic factors, lifestyle factors, and markers of the metabolic syndrome
- The comorbidity between depression and anxiety may be the most important factor
  - Comorbid anxiety might play a role in the increased activation of the HPA axis observed in patients with depression
- Diabetes did not predict subsequent symptoms of depression or anxiety

Engum J. Psychosom Res 2007;62:31-8
Premenstrual dysphoric disorder

Dysphoria, irritability, anxiety/tension are the main ps. symptoms

React with panic to lactate challenge

Respond to intermittent SSRIs

Irritable bowel syndrome

IBS is associated with fibromyalgia, chronic pain, depression and anxiety disorders.

26% of GAD patients in an anxiety clinic had IBS, 22% of panic, and 25% of depressed.

Gros et al. J Anx Disord 2009;23:290-6
Dermatology

• Pruritus, urticaria, angioedema, flushing, perspiration
• Psoriasis, atopic eczema
• Dermatitis artefacta, trichotillomania
• Body dysmorphic disorder
• Dissociation, somatization, conversion

Late-life anxiety and depression

Ivan Albright 1897-1983
Psychiatric diagnoses among 85-year-olds in Göteborg without dementia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Men n=104 procent</th>
<th>Women n=243 procent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phobias</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>OCD</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>GAD/Panic</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Depression</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Psychosis</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Any of the above</td>
<td>29</td>
<td>37</td>
</tr>
</tbody>
</table>

Ingmar Skoog dissertation 1993
Benzodiazepine update

Christer Allgulander and David Nutt:
Benzodiazepines

Springer, August 2010
$949

Benzodiazepines for these reasons

- Offer rapid anxiolytic effect
- Reinforcing only in predisposed substance abusers
- Have important clinical utility
- Are safe in overdose
- Are inexpensive
Benzodiazepine indications

- Insomnia
- Anxiety disorders (GAD, specific phobias, panic disorder, social anxiety disorder)
- Anxiety in depression (as an adjunct at initiation of antidepressant therapy)
- Schizophrenia (catatonic type, and for rapid tranquillization)
- Acute mania
- Organic brain syndrome (acute, e.g. delirium tremens, and chronic, e.g. dementia)
- Alcohol and sedative withdrawal
- Suicidal patients with prominent anxiety symptoms
- Adjustment disorders
- Avoidant personality disorder
- Status epilepticus
- Adjuvans in anaesthesia
- Tardive dyskinesia, akathisia
- Spasticity (e.g. spastic paraplegia), acute torticollis

*Contraindications: Myasthenia gravis, sleep apnea, severe pulmonary disease*
Benzodiazepine memory effects

In a meta-analysis of tested subjects after a mean of 10 years of BZ treatment, significant impairment was found in all cognitive domains.

Barker et al. Arch Clin Neuropsychol 2004;19;437-54
How to prescribe benzodiazepines

- Establish disabling anxiety/insomnia.
- Inform about reduced reaction time.
- Advise against concurrent alcohol intake.
- Use effective doses, regular or as needed.
- Monitor potential tolerance development.
- Ask for memory impairment, anterograde amnesia.
- Do not prescribe BZs to unreliable patients.

(Forging prescriptions, multiple prescribers, web).

Allgulander & Msghina. Läkartidn 2011;108:2025-29
Baldwin DS et al. J Psychopharmacol 2013;27:967-71
Ethnicity

Pharmacogenetics

Illness attribution
80% of the world population subscribe to traditional medicine (WHO)

Muti medicine, Durban, 2006
Adherence to pharmacotherapy
“All real helpfulness starts with humility regarding the person I want to help and because of this I must understand that helping is not to reign but to serve”

Søren Kirkegaard, 1813-1855
Patient Delay

Syndromal levels of symptoms & coping

Mild/no symptoms & coping/functioning

Syndromal levels of symptoms & NOT coping

Help!!!

May be precipitated by a life event
# Duration of GAD Before Treatment

100 outpatients with GAD in Mood Disorders Clinic in Milan\(^1\)

<table>
<thead>
<tr>
<th>Duration of GAD</th>
<th>Mean (SD) duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before receiving treatment with benzodiazepines</td>
<td>12.8 (7) years</td>
</tr>
<tr>
<td>Before receiving treatment with antidepressants</td>
<td>58 (94) months</td>
</tr>
<tr>
<td></td>
<td>84 (99) months</td>
</tr>
</tbody>
</table>

Altamura et al. CNS Spectr 2008;13:415-22
Getting the Patient on Board

Not yet a patient:

• Stigma
• Illness attribution
• Cannot afford treatment
Getting the Patient on Board II

First visit diagnosed with GAD:
• Fear of addiction
• Worry about side effects (nocebo)
• Favors psychotherapy
• Internet expert (bibliotherapy)
While on successful treatment:

- Sexual side effects
- Weight gain
- Adherence
- How long do I continue treatment?
Attitude Survey in Sweden, 1987

People in general regarded antidepressants/anxiolytics to be as hazardous as alcohol, and more hazardous than cars and nuclear power.

Malmfors et al. Sv Farmac Tidskr 1988;92:31-7
Fear of Addiction: 
Defeat Depression Campaign, UK 1992

Most (78%) thought that antidepressants were addictive, and only 16% thought that they should be given to depressed people.

Priest et al. BMJ 1996;313:858-9
Thomas Szasz and Tom Cruise
Hollywood, 2004
Adherence and Outcome: Sertraline for Depression – Response Rate at 24 Weeks

Drug plasma assays taken in 792 primary care patients

Responder at week 24: MADRS ≥ 50% reduction, CGI-Severity of normal to mildly ill, and CGI-Improvement of much or very much improved

Reis et al. J Clin Psychopharmacol 2010;30:746-8
Tell the Patient Who Starts Treatment

• Take medication daily
• Antidepressants/anxiolytics may take some weeks to work
• Continue taking medication even when feeling improved
• Do not stop taking medication without checking with the prescribing physician
• Inform about potential side effects
• Schedule pleasant activities
Addressing addiction concerns

Tell the patient that

• Many types of medicines cause withdrawal symptoms, such as antihypertensives and cortisone
• Addiction is craving for euphoria, getting high or sedated, not symptom amelioration
• Addiction is tolerance; a need to increase the dose
• Tolerance and craving do not exist with medicines approved for GAD
The End