Breathing Deeply: Managing COPD and Comorbid Depression

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Accreditation
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Nurses: N-781

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Faculty Disclosure
Dr. Stolte has no actual or potential conflicts of interest in relation to this program.

Learning Objectives
- List prevalence, severity, causes, and exacerbations of common comorbidities that complicate the treatment of COPD patients, with an emphasis on the relationship between COPD and comorbid depression.
- List classes, efficacy, and safety of commonly used medications to treat the spectrum of COPD disorders.
- Create strategies that empower the pharmacist to manage patients with COPD, understanding the profound role of communicating with the patient for improved outcomes and adherence.

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Objectives
- At the completion of this activity, the participant will be able to:
  - List prevalence, severity, causes, and exacerbations of common co-morbidities that complicate the treatment of COPD patients, with an emphasis on the relationship between COPD and co-morbid depression.
  - List classes, efficacy, and safety of commonly used medications to treat the spectrum of COPD disorders.
  - Create strategies that empower the pharmacist to manage patients with COPD, understanding the profound role of communicating with the patient for improved outcomes and adherence.

COPD Definition
- COPD is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.
- From GOLD – Global Initiative for Chronic Obstructive Lung Disease
COPD Causes

• Cigarette smoking accounts for 85-90% of COPD cases
• Dependent on:
  – Age started
  – Pack years (Packs/day x number of years smoked)
  – Current status
• Passive exposure (Secondhand smoke)
  – Increases total lung burden of inhaled particles or gas, leading to respiratory symptoms

COPD Risk Factors

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Host Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental tobacco smoke</td>
<td>Genetic predisposition (alpha, antitrypsin deficiency)</td>
</tr>
<tr>
<td>Occupational dusts and chemicals</td>
<td>Airway hyperresponsiveness</td>
</tr>
<tr>
<td>Indoor and outdoor air pollution</td>
<td>Impaired lung growth</td>
</tr>
</tbody>
</table>

Other risk factors include: gender, advanced age, low SES, ethnicity, repeated childhood respiratory infections, lung growth and development, nutrition

Alpha, antitrypsin deficiency accounts for less than 1% of COPD cases. Screening should be performed for all patients less than 45 yo who develop COPD and have family history of COPD

COPD Epidemiology

• 6th leading cause of death
  – 124,000 annually
• 12.1 million with COPD diagnosis
  – Approximately 4-5:1, Chronic bronchitis:Emphysema
• More common in men than women
  – 82 vs. 57/100,000
• More common in Caucasians than blacks
  – 70 vs. 43/100,000
• 700,000 hospital admissions
• 1.5 million ER visits
• Economic Impact - $37.2 billion
  – $20.9 billion direct, $16.3 billion indirect

COPD Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV1/FVC</th>
<th>FEV1/LT predicted</th>
<th>COPD severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>FEV1/FVC &gt; 0.70</td>
<td>FEV1 &gt; 80% predicted</td>
<td>Mild</td>
</tr>
<tr>
<td>II</td>
<td>FEV1/FVC &lt; 0.70</td>
<td>FEV1 &gt; 80% predicted</td>
<td>Moderate</td>
</tr>
<tr>
<td>III</td>
<td>FEV1 &lt; 80% predicted</td>
<td>FEV1 &lt; 80% predicted</td>
<td>Severe</td>
</tr>
<tr>
<td>IV</td>
<td>FEV1 &lt; 80% predicted</td>
<td>FEV1 &lt; 80% predicted</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

Active treatment of risk factors: Advise cessation of smoking. Add short-acting bronchodilators when needed. Add regular treatment with one or more long-acting bronchodilators if needed. Additional gastroesophageal reflux disease may be present. Consider surgical treatments.
Pharmacological Interventions

- Bronchodilators
  - Short-acting - albuterol
  - Long-acting – salmeterol, formoterol
- Anticholinergics
  - Short-acting - ipratropium
  - Long-acting - tiotropium
- Methylxanthines - theophylline
- Inhaled corticosteroids - budesonide
- Systemic corticosteroids - prednisone
- Alpha₁ antitrypsin replacement therapy
- Oxygen therapy

Pharmacologic Management

- **General Principles**
  - None of the existing medications for COPD modify long-term decline in lung function
  - Bronchodilator medications are essential to the symptomatic management of COPD
  - Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators
  - The addition of regular treatment with inhaled CSs to bronchodilators is appropriate for symptomatic COPD patients (Stage III and IV) and repeated exacerbations

General Principles – continued

- Chronic treatment with systemic CSs should be avoided because of an unfavorable benefit to risk ratio
- The long-term administration of oxygen therapy (>15 hours/day) to patients with chronic respiratory failure has been shown to increase survival

COPD and Depression

- Co-morbid depression and depressive symptoms prevalent in COPD patients
  - Even when only looking at first episode of depression after COPD diagnosis
  - Incidence of depression twice as high with COPD compared to non-COPD population
  - 90% in end-stage COPD (52% with end-stage lung cancer)
- Prevalence rate for co-morbidity = 40%
- Poor rate of depression detection in COPD patients
  - Less than 50% are recognized
- Current consensus statements and guidelines emphasize the need for depression assessment and treatment in COPD patients
Risk Factors For Co-Morbid COPD and Depression

- More common in:
  - Younger patients
  - Women
  - Current smokers
    - Even when compared to smokers without COPD
    - Current cigarette smoking, itself, increases incidence of depression
    - May be mainly attributed to failure to quit

Consequences of Co-Morbid COPD and Depression

- Negative course of COPD disease
  - Increased mortality
  - Increased exacerbation frequency
  - Increased hospitalizations
  - Decreased functional status
    - Depression may be a better predictor than lung function
    - Decreased quality of life (QoL)
    - Decreased activity level

Treatment of Co-Morbid COPD and Depression

- Nonpharmacological
  - COPD Education
  - Cognitive-Behavioral Therapy (CBT)

- Pharmacological
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)

COPD Education

- COPD education is an important first step for COPD treatment
  - May enhance perceived self-efficacy
    - Self-efficacy – the belief that one is capable of performing in a manner that allows for achievement of goals
    - Increases motivation to engage in any form of treatment (improved adherence)

- COPD education can be provided by pharmacists. No one else is doing this!
Cognitive-Behavioral Therapy (CBT)

- **Definition**
  - A form of psychotherapy that emphasizes the role of thinking in how we feel and what we do
- **General term**
  - A classification of therapies with similarities
    - Rational Emotive Behavior Therapy, Rational Behavior Therapy, Rational Living Therapy, Cognitive Therapy, and Dialectic Behavior Therapy

Cognitive-Behavioral Therapy

- Most have the following characteristics:
  - Based on a cognitive model of emotional response
    - Thoughts cause feeling and behaviors
    - External factors do not
  - CBT is more brief than other forms of psychotherapy, and it is time-limited
    - Average number of sessions = 16, psychoanalysis can take years
    - Incorporates homework assignments
    - Therapist and client decide end of therapy

Cognitive-Behavioral Therapy Characteristics (Continued)

- A sound therapeutic relationship is necessary for therapy, but it is NOT the focus of therapy
  - Therapists focus on teaching self-counseling skills
- CBT is a collaborative effort between therapist and client
- CBT is based on aspects of stoic philosophy
  - Emphasizes stoicism
  - In undesirable situations, at worst, client feels calm
  - If feel upset about problem, two problems are created

Cognitive-Behavioral Therapy Characteristics (Continued)

- CBT uses the Socratic method
  - CBT therapists ask questions and teach clients to ask questions of themselves
  - “How do I know that person is upset with me? Could he/she be upset with someone/something else?”
- CBT is structured and directive
  - Specific agenda for each session
  - CBT therapists teach clients “how to do”
Cognitive-Behavior Therapy Characteristics (Continued)

- CBT is based on an educational model
  - Assumes most emotional and behavioral reactions are learned
  - “Unlearn” unwanted reactions, learn new reactions
- CBT theory and techniques rely on the Inductive Method
  - Our thoughts are NOT facts
  - Our thoughts are guesses that can be questioned and tested
- Homework is a central feature of CBT
  - CBT therapists assign readings and require practice of learned techniques

CBT Effectiveness Summary

- No studies in exclusively COPD with co-morbid depression patients
- 12 total studies, 6 randomized, controlled
- 4 of 6 randomized, controlled studies showed significantly improved depression scores compared to control group.
- All 6 randomized, controlled studies showed significant symptom improvement

Role of Pharmacists in CBT

- Be aware of it!
- There is more to treatment than meds
- Develop a plan for referral for patients who may benefit
- Don’t underestimate the importance of self-efficacy
  - Better adherence
  - Better outcomes

TCA Effectiveness

- Five studies identified, all dated
- Overall, most have small sample size
- All studies showed high drop-out rates
  - Most drop-outs due to medication side effects
- Only 2 studies used DSM criteria to diagnose depression
- Co-morbid symptoms of anxiety not controlled for in studies
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Gordon et al. (1985)
- Randomized, double-blind crossover
- N=13 (6 completed), outpatient, stable COPD, stage III
- None met DSM criteria for depression
- Desipramine for 8 weeks and placebo for 8 weeks, initial dose 25 mg/day, increased weekly as tolerated (NTE 100 mg/day)
- Outcomes - Beck DI and Zung self-rating depression scale
- Depression scores improved significantly with placebo and treatment

Light et al. (1986)
- Randomized, double-blind crossover trial
- N=12 (9 completed), outpatient, stage III COPD, high levels of depression
- Doxepin HCl for 6 weeks, placebo for 6 weeks, doses as tolerated (NTE 105 mg/day)
- Outcomes - Beck DI, 12 min walking distance, Spielberger’s state-trait anxiety inventory
- No significant improvement in exercise capacity, depression scores, anxiety scores

Sharma et al. (1988)
- Double-blind
- N=10 consecutive COPD patients, all stages evaluated for depression
- Imipramine-diazepam combination
- Helped depressed patients recover faster
  - Diazepam may trigger resp. failure

Borson et al. (1992)
- Randomized, double-blind, placebo controlled
- N=36 (30 completed, 17 placebo) stage II and III COPD and DSM-diagnosed co-morbid depressive disorder, 83% with anxiety
- Nortriptyline vs. placebo for 12 weeks, 0.25-1 mg/kg increased NTE 1 mg/kg
- Outcomes - Clinical Global Improvement Scale (CGI), Hamilton, Patient-rated Anxiety Scale (PRAS), 12MWD, Pulmonary function Status instrument (PFSI), Sickness impact profile (SIP), Dyspnea questionnaire
- Nortriptyline significantly improved depression, anxiety, resp. symptoms, physical comfort, and daily functioning
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### Strom et al. (1995)
- Randomized, double-blind, placebo-controlled
- N=26 (12 placebo, 5 completed) stable COPD patients at least stage II, mild to moderate hypoxemia
- Protriptyline vs. placebo for 12 weeks, 10 mg/day
- Outcomes - Hospital anxiety and depression scale (HADS), Mood adjective checklist (MACL), SIP, Dyspnea scale
- No improvement in depression or anxiety scores, arterial blood gases, spirometry values, dyspnea, or QoL
- High rate of anticholinergic effects

Strom K et al., Eur Respir J, 1995;8:425-29.

### SSRI Effectiveness
- Six studies identified (more recent, but dated)
- Overall, most have small sample sizes
- Drop-out rates high for many
- None used DSM criteria for depression
- Co-morbid anxiety either not controlled for or not excluded

### Papp et al. (1995)
- Pilot study, descriptive
- N=6 consecutive COPD outpatients, 3 with co-morbid anxiety or depression
- Sertraline for 6 weeks, 12.5 mg/day to start, increased to 100 mg/day during first 2 weeks
- Sertraline well tolerated, N=5 showed improvement in activities of daily living (ADLs), no improvement in physiological parameters, subjective improvement in psychiatric conditions


### Smoller et al. (1998)
- Case reports (6 retrospective, 1 prospective)
- N=7 with obstructive airway disease (included asthma)
  - Psychiatric conditions varied
  - Sertraline (25-100 mg/day) added to regular medication – varying durations
- Outcomes – varied across patients
- Improvements in dyspnea, but not in FEV₁, Some reported exercise tolerance improvement, mood, and anxiety.

**Evans et al. (1997)**
- Randomized, double-blind, placebo controlled
- N=82 (42 completed, 21 placebo) acute geriatric inpatients with depression, 38 with respiratory diseases
- Fluoxetine 20 mg/day vs. placebo for 8 weeks
- Outcomes – Hamilton Depression Rating Scale (HAMD), Evans Liverpool Depression Rating Scale (ELDRS), Geriatric Mental State (GMS)
- No significant difference in response rates, trend toward better response in treatment group after 8 weeks, Significantly more recovery from depression after 5 weeks of treatment


**Yohannes et al. (2001)**
- Single-blind, open
- N=57 COPD patients stage II-III and depression, 14 agreed to fluoxetine (72% refusal rate), 7 completed
- Fluoxetine 20 mg/day for 6 months
- Outcomes - GMS, Montgomery-Asperg depression rating scale (MADRS), Manchester respiratory activities of daily living questionnaire (MRADL), Breathing problems questionnaire (BPQ)
- 4/7 completers responded to fluoxetine, 5 withdrew due to adverse effects


**Lacasse et al. (2004)**
- Randomized, double-blind, placebo controlled
- N=23 (15 completed, 7 placebo) outpatients with COPD and depressive symptoms
- Paroxetine 10-20 mg/day vs. placebo for 12 weeks
- Outcomes - Geriatric depression scale (GDS), Short-form 36 (SF-36), Chronic respiratory questionnaire (CRQ)
- GDS improved significantly after paroxetine (not placebo), Significant improvements in emotion and mastery domains, Non-significant, but clinically important, improvements in dyspnea and fatigue.


**Eiser et al. (2005)**
- Randomized, double-blind, placebo-controlled
- N=28 stable outpatients with COPD stages II-III and depression (ICD-10 criteria for diagnosis)
- Paroxetine 20 mg/day vs. placebo for 6 weeks, unblinded paroxetine for 3 months
- Outcomes – Hospital anxiety and depression scale (HADS), BDI, MADRS, St. George’s respiratory questionnaire (SGRQ), 6-minute walking distance (6MWD)
- No significant difference between groups after 6 weeks blinded treatment, after 3 months unblinded, depression scores, walking distance, and QoL had significantly improved

### Overall Trial Limitations

- Not many trials, small sample sizes
- Mixed results
- Standard for diagnosis of depression not used (esp. DSM criteria)
- Many trials included non-depressed patients
- Depression and anxiety often included together
  - CBT treatment differs
  - Anxiety with depression = higher risk for depression treatment resistance, require longer duration of treatment for efficacy

### Conclusions

- Important issue
  - Under/Undiagnosed
  - High prevalence
- More trials needed – very limited
  - Larger sample sizes
  - COPD with co-morbid DSM-diagnosed depression
  - Exclude patients with anxiety
  - Standardized methodology
- COPD education should be included for all patients, regardless of intervention

### Role of Pharmacists in Pharmacotherapy of COPD with Co-Morbid Depression

- Provide COPD education
  - Resources:
    - NHLBI
    - American Lung Association
- Look for signs and symptoms
  - Often undiagnosed and/or untreated
  - Have referral plan in place
- Take a few minutes to talk with patients!