Pregabalin As A Treatment for Generalized Anxiety Disorder

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PGY III
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Background Information

• Approximately 18.1 percent of American adults 18 years or older have an anxiety disorder (Kessler RC, 2005)
  – High rate of comorbidity for a second anxiety disorder
  – Almost 75% of patients with an anxiety disorder experience their first episode by 21 yo

• Generalized anxiety disorder is the most common anxiety disorder presenting in primary care settings (Wittchen HT, 2002)
  – Only one third of patients with GAD are diagnosed in the primary care setting.
  – Majority of patients presenting to primary care settings experience more somatic symptoms, pain and insomnia
Background Information

- 12 year naturalist study showed the probability of achieving recovery was lower for GAD when compared to Panic Disorder and MDD (Bruce, 2005)
  - Of patients who did recover 45% experienced recurrence of sx’s
- 12 month community survey showed that the quality of life for patients with GAD was significantly poorer than patients with MDD (Kessler and Wittchen, 2000)
- The level of functional impairment in primary care patients with GAD was reported to be greater than patients with major medical illnesses including DM2, HTN, recent MI and CHF (Maki, 2003)
- Early treatment of GAD with medication may prevent or delay future episodes of major depression (Goodwin RD, 2002)
Pregabalin

• Approved for fibromyalgia, neuropathic pain, adjunctive therapy in adults with partial seizures

• Binds to alpha 2 delta subunit of voltage sensitive calcium channels
  – Effects the release of glutamate, substance P and NE

• Thought to have an effect on active anxiety circuits to reduce their activity and improve sx’s
Pregabalin

- Highly lipophilic and rapidly absorbed in the GI tract
- Achieves maximum plasma concentrations within 1.5 hours
- Thought to rapidly penetrate CNS based on animal studies
- Oral bioavailability of > 90%
- No known drug interactions or effects CYP450 systems
- No known protein binding
PICO Question

- **P**: Patients with GAD
- **I**: treated with pregabalin
- **C**: compared with placebo
- **O**: improve anxiety symptoms
Efficacy and Safety of Pregabalin in the Treatment of Generalized Anxiety Disorder

Stuart A. Montgomery, M.D. Ph.D., Kathy Tobias, M.D., Gwen L. Zombery, M.D.
Methods

• Conducted at 76 centers (52 were in primary care settings) in 5 European countries
• Participants were recruited from outpatient settings in general medical or psychiatric practices
• Inclusion criteria: Older than 18, met DSMIV criteria for primary GAD using the Mini-International Neuropsychiatric Interview
Methods

• Participants were required to have total score of ≥ 20 on HAM-A, score of ≥ 9 on the Covi Anxiety Scale and ≤ 7 on the Raskin Depression Scale

• Exclusion criteria:
  – No other primary Axis I diagnosis except Depressive Disorder NOS or dysthymia, Somatization Disorder or Simple Phobia
  – Clinically relevant medical illnesses
  – Patients considered at risk for suicide
  – Axis II diagnosis
  – Use of gabapentin or benzodiazepines 1 week prior to baseline visit
  – Use of psychotropics within two weeks of study entry
  – Ongoing psychodynamic or CBT
  – Use of beta blockers, corticosteroids (except topical or inhaled < 1000 micrograms), antihypertensives or psychotropics during the study
Methods: Study Design

- Patients were randomly assigned to 1 of 4 treatment groups for 6 weeks
  - Pregabalin 400 mg/day
    - Starting dose of 200 mg/day titrated to full dose by day 5
  - Pregabalin 600 mg/day
    - Starting dose of 150 mg/day titrated to full dose by day 7
  - Venlafaxine 75 mg/day
    - Starting dose was 37.5 mg BID
  - Matched placebo
- The 6 week double blind treatment was followed by 1 week double blind taper and follow up phase
Methods: Efficacy Analyses

- Primary measure of efficacy was a change in clinician rated HAM-A total score
  - Screening, baseline, study weeks 1, 2, 3, 4, 6
- Secondary efficacy
  - HAM-A scores total scores analyzed by week
  - Responder rate determined by ≥ 50% reduction from baseline HAM-A score
  - Clinical Global Impression Improvement Scale score and responder rate
  - Clinician rated Hamilton Rating Scale for Depression
  - Hospital Anxiety and Depression Scale
Methods: Safety and Tolerability Analyses

• Evaluated on patient report of adverse events at each clinic visit
  – Monitored for the nature, intensity and relationship to treatment

• At the beginning and end of the treatment visit
  – EKG
  – Physical exam
  – Laboratory work
Statistical Analyses

• Designed to enroll 95 evaluable patients per treatment group this sample size was estimated with a power of 85% to detect 3 point difference in the change in HAM-A score between either of the two pregabalin groups and the placebo using 2 sided t-test

• Primary efficacy and safety analyses were performed on the intent to treat population
  – Only pts with at least one postbaseline assessment were included in the efficacy analyses
  – Significant level was 0.05

• Last observation carried forward was used on all of the primary and secondary outcome measures for the planned analyses
Statistical Analyses

- Changes from baseline to endpoint in the HAM-A were compared using ANCOVA.
- Hochberg’s procedure was used to adjust for multiple comparisons for pregabalin vs placebo comparisons at endpoints.
- Time to onset of sustained improvement was defined as ≥ 30% reduction from baseline HAM-A score to the end of the study.
  - Time to onset of sustained response was determined in number of days from baseline to the initial double blind visit at which sustained HAM-A improvement was observed.
- Changes from baseline HAM-A psychic, HAM-A somatic, HAM-A ≥ 50% responders, HAM-D, HADS-A and HADS-D were also compared.
  - Psychic = anxiety, tension, worry.
  - Somatic = muscular somatic sx’s, GI, sensory somatic sx’s, autonomic sx’s.
Statistical Analyses

- CGI-I scores were compared using ANOVA
- Logistic regression was used to analyze responders by treatment group
Results

• 543 pts were screened
  – 421 were randomized and received meds
  – 76.5% completed the study
• 62% women
• Mean age was 44.1
• Mean baseline HAM-A ranged 26.0 to 27.4 (mod to severe)
• Significantly more patients with pregabalin 400 mg/day dose completed the study when compared to venlafaxine
Results

- Treatment with pregabalin was associated with overall improvement of GAD sx’s
  - Pregabalin 400 mg/day 0.38
  - Pregabalin 600 mg/day 0.31
  - Venlafaxine 75 mg/day 0.31
- Sustained improvement at week 1 was experienced by 33% of pregabalin 400 mg/day, 46% of pregabalin 600 mg/day and 23% of venlafaxine and 29% of placebo
- Proportion of patients with \( \geq 50\% \) reduction in HAM-A at endpoint was significant for pregabalin 400 mg/day and venlafaxine
  - 61 % with \( p = 0.02 \) pregabalin
  - 62 % with \( p = 0.01 \) venlafaxine
- Pregabalin at both doses showed greater improvement in HAM-A total score at week one than did venlafaxine in post hoc direct comparisons
  - 400 mg/day vs venlafaxine 75 mg/day \( p = 0.005 \)
  - 600 mg/day vs venlafaxine 75 mg/day \( p = 0.0002 \)
Results

• Significant efficacy compared to placebo was found at 1 week in both pregabalin groups, HAM-A psychic factor score.
• HAM-A somatic factor score only pregabalin 400 mg/day was associated with significant efficacy vs placebo at week 1 and LOCF endpoint.
• Patients treated with medications showed significantly greater improvement on LOCF endpoint compared to placebo on HAM-A item 1 (anxiety, worry) and item 2 (tension).
• Sleep disturbance was assessed in terms of improvement with insomnia and fatigue on wakening pregabalin showed an advantage over venlafaxine:
  – Pregabalin 400 mg/day -1.4, p < 0.001
  – Pregabalin 600 mg/day -1.4, p < 0.001
  – Venlafaxine 75 mg/day -1.0, p = 0.12
Results

• Change in patient’s overall status was evaluated by CGI-I
  – Treatment with pregabalin 400 mg/day and venlafaxine 75 mg/day were associated with significantly greater improvement than placebo in mean CGI-I score
  – Proportion of pts who were rated “much improved” or “very much improved” at the end of treatment was significantly greater in all treatment groups
Results: Tolerability

- Most common adverse events were somnolence, dizziness and nausea
- Fewer patients discontinued pregabalin or reported severe adverse events than venlafaxine group with $X^2 = 8.80$, $p < 0.01$
  - 20.4% for venlafaxine
  - 13.6% for pregabalin 600 mg/day
  - 9.9% for placebo
  - 6.2% for pregabalin 400 mg/day
- Median onset of adverse events developed quickly, with remission occurring during the first two weeks of dose stabilization
- No clinically significant changes in vital signs, lab values or EKG changes were observed
- Weight gain was dose dependent
  - 1.0 ± 2.1 kg (400 mg/day), 1.6 ±2.5 kg (600 mg/day)
Discussion

• At both dosages studied pregabalin was associated with significant endpoint improvements comparable to venlafaxine
  – Only 400 mg/day had significant efficacy on the primary (HAM-A) and secondary outcome measures (HAM-A psychic, HAM-A somatic and CGI-I)
• Significant advantage compared to placebo was observed at both dosages as early as the first week of assessment.
  – Rapid and sustained benefit from pregabalin
• In general pregabalin was well tolerated with few sustained adverse effects
<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized double blind placebo study</td>
<td>• Homogenous sample in terms of race</td>
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<tr>
<td>• Studied several fixed dosage of pregabalin</td>
<td>• Short length of study</td>
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<td>• Excluded patients with other predominant diagnoses and treatment with other psychotropic medications</td>
<td>• No follow up to see effects of medication</td>
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<tr>
<td>• Utilized multiple measures to determine efficacy</td>
<td>• Did not compare increased dose of venlafaxine to increased dose of pregabalin</td>
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<tr>
<td></td>
<td>• Did not exclude patients using substances</td>
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<td></td>
<td>• Small sample size per treatment group</td>
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Pregabalin for Treatment of Generalized Anxiety Disorder

Karl Rickles, MD; Mark H. Pollack, MD; Douglas E. Feltner, MD
Methods: Study Design

- Double blind placebo controlled of tolerability of three fixed doses of pregabalin vs alprazolam
  - Treatment with alprazolam was initiated at 0.5 mg/day, titrated to 1.0 mg/day on day 4 and 1.5 mg/day on day 7
  - Pregabalin 300 mg/day, 450 mg/day, 600 mg/day
    - Titrated to 450 mg/day on day 4
    - Titrated to 600 mg/day on day 7
    - Divided doses using a three times a day dosing
- Patients were randomized in groups of 10 for 4 weeks
- Completed 1 week drug free screening period
  - No placebo was given and prohibited medications were washed out
- At the conclusion of the 4 weeks medications were discontinued during 1 week taper and patients were observed during 1 week for discontinuation symptoms
Methods: Patient Selection

• Recruited through clinic referrals and from media advertisements in the local media

• Inclusion criteria: older than 18 years old, met criteria for DMS-IV GAD on structured Mini International Neuropsychiatric Interview, baseline HAM-A ≥ 20 and 9 or greater on Covi Anxiety Scale
Methods: Patient Selection

- Exclusion Criteria
  - Raskin Depression scale > 7
  - Fertile women with positive pregnancy test, not using medically accepted contraceptive or currently nursing
  - Current or past history of Bipolar Disorder, Psychotic Disorders, Dementia or Factitious Disorder
  - Current history of MDD, OCD, Panic Disorder, PTSD, Acute Stress Disorder, Eating Disorder, Substance Use Disorder
  - Positive urine drug screen including benzodiazepines
  - Any clinically significant acute or unstable medical conditions
  - Psychotherapy for GAD
  - Suicide risk either currently or based on history
  - Current or past history of seizure disorder or pts requiring anticonvulsant tx
  - Concomitant use of psychototropic medication
Method: Efficacy Measures

- Primary efficacy measure: change from baseline to end point in total score of clinician rated HAM-A
  - Baseline visit, weeks 1, 2, 3 and 4
- Secondary efficacy measures
  - HAM-D
    - Baseline and week 4
  - Clinical Global Impression Improvement Scale
    - Weeks 1, 2, 3, 4
  - HAM-A psychic and somatic anxiety factors
  - Items 1 (anxiety/worry) and 2 (tension)
  - Endicott Work Productivity Scale
Methods: Safety and Tolerability Measures

- Spontaneously reported or observed adverse events were recorded
- Concomitant medications were recorded for daily dosage, start/stop dates and reason for use
- Compliance was monitored by counts of returned medication
- Physician Withdrawal Checklist was used at week 4 and at two week follow up
Methods: Statistical Analyses

• Sample size of 97 participants per treatment group would provide 85% power to detect mean difference of 3.5 in the HAM-A score at treatment end between placebo and pregabalin groups.

• Weekly HAM-A change scores were analyzed by ANCOVA using a model including the effects of treatment and center with baseline HAM-A as the covariance.

• HAM-A change score from baseline to endpoint were analyzed with ANCOVA:
  – Least square means and 95% confidence interval were calculated and an adjustment was made for multiple comparisons was used to test the treatment effect in each pregabalin vs placebo group.
Methods: Statistical Analyses

• Treatment effects on the total HAM-D score, HAM-A somatic and psychic anxiety subscales, and HAM-A anxiety and tension items were evaluated with ANCOVA.

• Patients’ response to pregabalin was evaluated by analyzing the percentage of HAM-A and CGI-I responders:
  – Patients with a 50% or greater decrease in HAM-A total score from baseline.
  – CGI-I responders were defined as “very much improved” or “much improved” at end point.

• Logistic regression adjusting for center was performed to compare the HAM-A and CGI-I responders by treatment group to the ITT population.
Methods: Statistical Analyses

• Rebound anxiety was assessed post hoc by comparing change in HAM-A total score from week 4 visit to follow up visit 1 week after treatment and 2 weeks after treatment
  – Defined as HAM-A score greater than the baseline value at the first follow up visit with a subsequent decrease in HAM-A score by the second follow up visit
Results: Patient Characteristics

- 696 were screened ---> 454 were randomized and received study medication
- 434 composed sample
- Sample characteristics
  - 68% Caucasian
  - Mean age 39
  - 58% female
Results: Efficacy and Endpoints

- For the primary endpoint as well as secondary endpoint measures showed that all three doses of pregabalin and alprazolam had significantly greater efficacy than placebo
  - Only exception was pregabalin 450 mg/day and alprazolam did not show statistical significance with HAM-A somatic anxiety factor
- Significantly more patients treated with 300 mg/day and 600 mg/day of pregabalin were treatment responders compared to placebo
- Significantly more patients taking pregabalin 300 mg/day were CGI-I and HAM-A responders compared to alprazolam (p<0.05)
Results

Dagger = $p < 0.05$ vs alprazolam

Asterisk = $p < 0.001$ vs placebo

Double dagger = $p < 0.10$ vs placebo

Section mark = $p < 0.01$ vs placebo

Parallel mark = $p < 0.05$ vs placebo
Results: Efficacy and Endpoints

- HAM-A total score for pregabalin doses 300 mg/day and 600 mg/day demonstrated greater improvement at one week than alprazolam (p < 0.05)
- Mean baseline HAM-D score was 13
- Endicott Work Productivity Scale mean score was 35.7 +/- 1.8 for placebo group to 39.4 +/- 1.9 for patients in the 5 treatment groups
Results: Tolerability and Safety

- Pregabalin was well tolerated at the three doses
  - Common side effects were somnolence, dry mouth and dizziness
  - Rate of discontinuation because of adverse events were 3% (300 mg), 5% (450 mg), 15% (600 mg), 14% alprazolam, 10% placebo
- Mean PWC score was similar across all treatment groups at the first follow up visit and second follow up visit except pregabalin 600 mg
  - Highest dose of medication showed increase in PWC 19.4 +/- 1.24 compared to placebo (P < 0.04)
- Weight gain dose dependent
  - 1.1 ± 0.2 kg (300 mg/day), 1.4 ± 0.2 kg (450 mg/day), 1.9 ± 0.2 kg (600 mg/day)
Discussion

• Pregabalin at all 3 doses showed significant end point improvement in HAM-A scores
  – Improvement in somatic and psychic HAM-A items
• Early onset of anxiolytic effect
• Well tolerated
  – Adverse effects showing tolerance within two weeks of initiating treatment
• Pregabalin treatment group showed dose dependent weight increase
• The increase in PWC scores at the second follow up visit with pregabalin 600 mg was not clinically significant
• Pregabalin 300 mg/d demonstrated efficacy comparable or better than higher doses and alprazolam
  – Lowest attrition rate
Strengths

• Double blind randomized placebo
• Studied three doses of target medication
• Used multiple measures to evaluate efficacy
• Excluded patients with Axis I

Limitations

• Short length of study
• Funded by Pfizer
• Did not provide detailed characteristics of sample population
• Compared varying doses of pregabalin with one dose of alprazolam
• Small sample population
Long-term Efficacy of Pregabalin in Generalized Anxiety Disorder

Douglas Feltner, Hans-Ulrich Wittchen, Richard Kavoussi
Methods: Study Design

- Multicenter randomized double blind fixed dose placebo controlled parallel group study
- Four phases
  - 1 week screening phase
  - 8 week open label acute tx phase
  - 24 week blind relapse prevention phase
  - 2 week discontinuation assessment phase
Methods: Patients

• Recruited through local advertisements and clinical referrals
• Inclusion criteria
  – ≥ 18 years old
  – DSMIV criteria of GAD with 1 year duration
  – HAM-A ≥ 20 at baseline and screening visits
  – Covi-Anxiety Scale ≥ 9
  – Raskin Depression Scale ≤ 7
Methods: Patients

• Exclusion criteria
  – Seizure Disorder or history of Bipolar Disorder, Factitious Disorder, Psychotic Disorder or Schizophrenia
  – History of significant Axis 1 disorder in the last 6 months not including Specific Phobia, Dysthymia, Depression NOS
  – Using any psychotropic medications within two weeks of first visit
  – At risk for suicide
  – Pregnant or lactating
  – Positive UDS
  – Psychotherapy for GAD unless it was ≥ 3 months
Methods: Treatment

- Pregabalin 300 mg/day dosed TID
  - Titrated to 450 mg/day until 8th week
- Randomized to receive 450 mg/day or placebo
  - If met criteria of ≥ 50% reduction from baseline HAM-A total score and HAM-A total score ≤ 11 at the end of two of three final visits
  - Treatment continued for up to 6 months or until patient relapsed or discontinued treatment
Methods: Efficacy Assessments

- Primary efficacy measure was time to relapse
  - Relapse was defined by
    - HAM-A total score ≥ 20 and met criteria for GAD by MINI at two successive visits 1 week apart
    - Rated “much worse” or “very much worse” on CGI-I scale and met criteria for GAD by MINI at two successive visits 1 week apart
    - Sx’s worsened requiring intervention
Methods: Efficacy Assessments

• Secondary Assessments
  – Changes in anxiety sx’s reflected by total score of HAM-A
  – Change in Depression sx’s reflected by HAM-D total score
    • Administered at the beginning of open label and double blind phases and end of double blind phase and discontinuation
  – Change in impairment reflected by Sheehan Disability Scale
    • Beginning of open label phase, weeks 4, 8, 10, 12, 32
  – Change in severity of sx’s on CGI-Severity scale
    • Beginning of open label phase and weeks 1,2,4,6,8,10,12, 16, 20, 24, 28 and 32
Methods: Safety Assessments

- Adverse events were monitored and assessed for duration, intensity and relationship to treatment
- PWC was administered at termination of double blind phase and at each of the two weekly visits during discontinuation phase
  - Assessed GI, mood, sleep, motor, somatic, cognition, perception
- During double blind phase discontinuation emergent signs and sx’s were assessed weekly for the first two weeks of the double blind phase
  - Discontinuation emergent signs were defined as adverse events that worsened or newly appeared during the first two weeks
Statistical Analysis

• Power calculation indicated sample size of 322 patients would provide 90% power to detect 20% difference in relapse rates between treatment groups at 6 months
  – Assuming premature discontinuation rate of 20% and relapse rate of 50% with placebo

• Primary efficacy measure was comparison of time to relapse between treatment groups using Kaplan-Meier time-to-event methods and log rank for significance
Statistical Analysis

- Analyses of secondary outcomes HAM-A, HAM-D, CGI-S, SDS were performed using ANCOVA with LOCF endpoint scores as the dependent variables
  - Double blind phase baseline score as the covariate

- Changes on PWC from the beginning of discontinuation phase to each of the assessments during discontinuation were evaluated using ANCOVA
  - Scores at the beginning of discontinuation phase as the covariate
Results

- 859 screened ⇔ 624 enrolled ⇔ 339 completed open label ⇔ ITT population 338 (168 pregabalin and 170 placebo)
  - 42.3% pregabalin and 65.3% placebo met relapse criteria
  - 21% pregabalin and 15.3% placebo discontinued prematurely
    - Adverse events, withdrew consent, lost to follow up, other reasons
Results

- 85% Caucasian, 58% female
- Mean age 37.3 years
- Mean duration of GAD 11 years
- No significant differences in terms of demographic variables between treatment and placebo groups
Results

- Efficacy of pregabalin in preventing or slowing relapse of anxiety was significant
  - Relapse occurred less often and later than placebo
  - 25% of placebo group relapsed by day 14 compared to day 25 for treatment group
Results

• Pregabalin was significantly more effective than placebo in maintaining the reductions in the anxiety symptoms and improvements in functional status
  – Mean CGI-S score increased from 1.9 to 3.7 in placebo to 1.9 to 3.0 in treatment group
  – Pregabalin was more effective than placebo in maintaining a reduced level of depressive sx’s associated with GAD assessed using HAM-D
Results

- Open label tx improved functioning in all three domains (work, family, social)
- Pregabalin was more effective in maintaining these improvements
  - Mean SDS social score increased from 2.1 to 2.4 with placebo vs decreased from 2.0 to 1.7 with pregabalin
  - Mean SDS family score increased from 2.2 to 2.4 with placebo vs decreased from 2.3 to 1.5 with pregabalin
  - Mean SDS work score increased from 2.1 to 2.4 with placebo vs decreased from 2.0 to 1.4 with pregabalin
Results

• During open label phase most common adverse effects were somnolence, dizziness, dry mouth, euphoria, weight gain
  – Were usually rated mild to moderate and remitted within a few weeks

• During double blind phase
  – 4 in placebo and 10 in pregabalin group discontinued because of side effects
  – No clinically meaningful changes in lab values or vital signs were observed
  – No treatment related serious adverse events or deaths observed
Results

• For both groups the most common moderate to severe symptoms reported on PWC during discontinuation were anxiety, nervousness, irritability, and insomnia
  – For pregabalin the greatest increases from termination to discontinuation phase visits were fatigue, lethargy, lack of energy.
  – At the two follow up visits no difference between PWC scores
  – 25% of patient from placebo and 28% from pregabalin group experienced adverse events during discontinuation phase
  – Most common discontinuation emergent signs and sx’s in patients treated with pregabalin were nausea, insomnia and diarrhea
Discussion

- Fixed daily dose of pregabalin 450 mg/day is more effective than placebo in preventing relapse in patients with GAD
  - Sustained improvements with degree of impairment and total anxiety sx’s experienced
  - Sustained improvement with depressive sx’s
- Pregabalin was well tolerated with mild to moderate adverse effects usually remitting within several weeks
- Few problems with withdrawal from pregabalin
  - Two weeks into the discontinuation phase only one moderate to severe symptom, diarrhea, was more common compared to placebo
Strengths
- Double blind placebo phase of the trial
- Demographics of sample was close to US population
- Used multiple measures for efficacy
- Excluded patients with positive UDS

Limitations
- High attrition rate
- Did not vary doses of pregabalin
- Short length of double blind maintenance
Clinical Relevance

• Given the data available pregabalin appears to be a medication that can be used in GAD in the short term or as an adjunct anxiolytic
  – Well tolerated
  – Would most likely use medication will titrating SSRI or SNRI
  – Can also use medication in patients with medical comorbidities