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Seroquel

- General
  - Generic name is quetiapine
  - Introduced 1997; Seroquel XR released in 2007
- Evidence of safety and efficacy
  - FDA-approval
    - Adult bipolar mania as monotherapy or adjunctive therapy in 2004
    - Adult bipolar I or II depression in 2006
    - May soon be FDA-approved as monotherapy for unipolar depression and separately as monotherapy for generalized anxiety disorder
    - May soon be FDA-approved for as an augmentor to lithium and valproic acid in the treatment of mania.
    - Treatment of schizophrenia in adults
  - Adults
    - Mania
      - Yatham et al, 2007: Seroquel vs. placebo as add-on therapy to lithium (mostly) or Depakote for mania; 211 patients; 6 weeks; slight improvement of Seroquel over lithium in symptoms; response rate 72% with Seroquel vs. 57% placebo; remission rate 68% with Seroquel vs. 57% placebo.
      - Calabrese: 12-week placebo-controlled, RCT for adults with mania: Seroquel (average dose 576 mg/day) 48% response rate, placebo 31%.
      - Pae, 2005: 6 month treatment with adjunctive Seroquel for mania; safe and effective.
      - Mullen, 2003: evidence of safety and efficacy in the adjunctive treatment of mania
      - Shaw, 2001: 8 week open label study, safe and effective
    - Bipolar depression
      - NNT 6 for response
        - NNH 6 for sedation, 19 for clinically significant weight gain
      - Young et al, 2010: 802 patients on Seroquel 300 vs. Seroquel 600 vs. lithium vs. placebo; both doses of Seroquel equally effective, more than lithium or placebo.
      - Thase et al, 2006: Seroquel 300 or 600 mg more effective than placebo
      - Hirschfeld et al, 2006: Seroquel vs. placebo in bipolar I or II depression—improvement by week 1; separate study demonstrated reduction in anxiety in bipolar I but not bipolar II
      - Suppes, 2005: 181 patients with bipolar II depression; 300 mg/day vs. 600 mg/day vs. placebo; 8 weeks, RCT, double-blind
        - Both Seroquel groups were effective; 22% withdrew due to adverse events with 300 mg, 13% with 600, 3% with placebo
        - Effective in rapid cycling too
      - Calabrese, 2005: Randomized, double-blind, placebo-controlled trial of Seroquel for Bipolar I or II depression; 542 patients, 300 versus 600 mg Seroquel versus placebo; Seroquel (either dose) nearly twice as effective, well-tolerated, with 3.2% treatment-emergent mania (versus 3.9% with placebo), independent of rapid cycling.
      - Calabrese, 2004: randomized, parallel-group, placebo-controlled trial of Seroquel in bipolar I, II depression with and without rapid cycling: effective regardless of rapid cycling.
    - Bipolar maintenance
      - Open-label study as monotherapy or add-on in rapid cycling bipolar I; evidence of efficacy; other evidence of efficacy in rapid cycling as add-on agent.
      - Open label use as adjuvant to Depakote found to be safe and effective.
      - Vieta, 2002: efficacy as add-on therapy to other mood stabilizers for rapid cycling bipolar disorder.
      - Ghaemi, 2001: open-label prospective study of 40 patients rapid cycling bipolar I with or without adjunctive mood stabilizer treatment; safe and effective.
    - Anxiety in bipolar disorder
      - Hirschfeld, 2006: monotherapy treatment of anxiety in patients with bipolar I or II depression, safe and effective (300 mg/day and 600 mg/day equivalent efficacy)
    - Treatment-resistant depression

        - May augment antidepressant efficacy in the treatment of depressive disorders and help attenuate the stress-induced increase in BDNF.
        - Bauer et al, 2009:
            - Add-on study to existing antidepressants
            - 150-300 mg/day
            - 493 people studied
            - Separation from placebo by week 1
            - Drop out due to adverse events was 7-12% for Seroquel vs. 4% for placebo
        - Doree et al 2007: open pilot study of Seroquel (400-800 mg/d) vs. lithium augmentation in treatment-resistant depression, 20 patients; improvement seen in both groups but plateaued with lithium (but not Seroquel) after one week; 8/10 met remission criteria with Seroquel vs 4/10 with lithium (plus 1 who met response but not remission criteria).
        - McIntyre et al, 2006: Seroquel added to Effexor XR for depression with co-morbid depression—mean dose 182 mg, onset of effect in one week
        - Dell'Osso et al, 2006: Seroquel augmentation of SSRI's (open-label case series) for treatment-resistant OCD; six month follow-up; safe and effective.
        - Pathak, 2005: adjunctive Seroquel for treatment-resistant depression in 10 adolescents, open-label; safe and effective
        - Also: Khullar et al, Mattingly et al, Earley et al, El-Khalil et al showed positive benefits
        - Open label study in 11 adults demonstrated efficacy
    - Borderline personality disorder
        - Bellino et al, 2006 (pilot study of 14 patients with borderline personality disorder, 11 of which completed the study): safe and effective
    - Schizophrenia/psychosis
        - Chen et al, 2010: maintenance treatment with Seroquel vs. discontinuation after one year of treatment in patients with remitted first episode psychosis
            - 178 patients
            - Seroquel 400 mg/day vs. placebo
            - Risk of relapse 41% with Seroquel and 79% with placebo
        - Kahn et al, 2007: Seroquel XR (once-daily dosing) vs. placebo in RCT, DB trial in schizophrenia; 588 patients (76% completed the trial); dosing: 400 , 600 and 800 mg daily doses studied
            - Seroquel XR significantly more effective than placebo
            - Side effects
                - Sedation/somnolence 7.1-11.6% vs. 1.7% placebo
                - Insomnia 6.2-11.5% vs. 19.5% placebo
                - Dizziness 5.3-8.8% vs. 0.8% placebo
        - McEvoy et al, 2007: 52-week DB, RCT Zyprexa vs. Seroquel vs. Risperdal in early psychosis—comparable efficacy and overall tolerability
        - Zhong et al, 2006, comparison of Seroquel and Risperdal in the treatment of schizophrenia: both safe and equally effective.
    - Generalized anxiety disorder
        - Sheehan et al, 2013:
            - Seroquel XR maintenance treatment and effects on functioning and sleep in GAD, analysis of patient-reported data from a randomized-withdrawal, DB, placebo-controlled study of Seroquel XR monotherapy in GAD; open-label run-in of 4-8 weeks then 12-18-week stabilization phase (Seroquel 50, 150, or 300 mg/day), after which randomized to continue of Seroquel XR or receive placebo for up to 52 weeks; 432 patients
            - Safe and effective (on many but not all measures)
        - Khan, Joyce et al, 2011:
            - 8 week active treatment plus 2 week discontinuation study, DB, RCT, 951 patients, Seroquel X% 50 vs. 150 vs. 300 vs. placebo
            - 50 mg and 150 mg doses both > placebo; not 300
            - Most common side effects: dry mouth, somnolence, sedation, dizziness, headache, fatigue
        - Gabriel, 2011
            - Adjunctive Seroquel XR to antidepressants in the treatment of partially responsive, poorly functioning patients with GAD; 24 patients, 12 weeks
            - Safe and effective
        - Joyce et al, 2008:
            - Seroquel XR 50-150 mg/day, monotherapy, safe and effective
            - 300 mg a little less efficacious

- Tic disorders
  - De Jonge et al, 2007: Tourette syndrome, 12 men, 12 weeks, 50-600 mg/day, average dose 205.8 mg/day, 3 patients dropped out due to side effects, those with the most severe symptoms improved the most
  - Two case reports in adults: 1) patient successfully treated for Tourette syndrome and mania (600 mg/day) and 2) patient with tic disorder (200 mg/day)
  - Two case reports in youth with Tourette syndrome
  - One open trial, 8 weeks, average dose 72.9 mg/day, 12 children, tic reduction of 30-100%
- Youth
  - Autism
    - 4 open-label studies
      - Hardan et al, 2005; 7-17 yo, 265-689 mg/day
        - 6/10 responded
      - Corson et al, 2004l 5-28 yo, 25-600 mg/day
        - 8/20 responded
      - Findling et al, 2004; 10-17 yo, 100-450 mg/day
        - 2/9 responded
      - Martin et al, 1999; 6-15 yo, 100-350 mg/day
        - 2/6 responded
    - Evidence not yet supportive of efficacy in autism.
  - Mood disorders other than bipolar I
    - DelBello et al, 2007: adolescents with mood disorders and family histories of bipolar disorder; 84 day study, single-blind, dose 300-600 mg, 20 youth: safe and effective with
      - 75% response rate
      - side effects:
        - sedation 55%
        - headache 25%
        - musculoskeletal 25%
        - stomach upset 25%
        - tremors 15%
        - congestion 15%
        - vomiting 10%
        - weight gain (8 lbs).
    - Singh et al, 2006: 20 adolescents with mood disorders (other than bipolar I disorder) who were offspring of parent(s) with bipolar disorder were compared to adolescents without mood disorders or family histories of bipolar disorder in their neurocognitive functioning; demonstrated some significant deficits which were improved on Seroquel
  - Treatment-resistant depression
    - Pathak, 2005: adjunctive Seroquel (150-300 mg) in adolescent treatment-resistant depression effective
      - Side effects:
        - Weight gain of 4.5-23 pounds during treatment
        - Sedation
  - Mania
    - DeBello, 2006: safe and effective in 50 adolescents average age 15 yo (range 14-16 yo) with bipolar disorder I with acute manic or mixed manic episode, Seroquel dose range 400-600 mg/day (titrated 100 mg x 1d→ 200 m x 1d→300 mg x 1d→400 mg. versus Depakote (blood levels 80-120, 90% of which achieved level of 90 by day 7)
      - 70-80% response rate and 60% remission rate for Seroquel
      - 40-55% response rate and 28% remission rate for Depakote.
    - DeBello, 2002: safe and efficacious as adjunctive to 30 inpatient adolescents with bipolar I disorder treated with Depakote: 87% response rate vs. 53% placebo
    - McConville, 2000 and 2003: 10 youths (7 with schizoaffective disorder, 3 with bipolar disorder), pharmacokinetic and efficacy study lasting up to 88 weeks duration, safe and effective at 300-800 mg/day.
  - Bipolar depression
    - DelBello et al, 2009, DBPC, 32 teens with bipolar depression, Seroquel 300-600 mg/d vs. placebo
      - Lack of evidence
    - DelBello et al, 2006, three studies investigating Seroquel in adolescent with bipolar disorder and depressive symptoms; 132 adolescents (30 youths (70% with mixed states) received Seroquel AND Depakote or Depakote alone; 50 youths (94% mixed state)

received Seroquel OR Depakote, 22 youths (mixed state OR familial risk for bipolar disorder) received Seroquel:
        - Seroquel (average dose 423 mg/d) with Depakote reduced depressive symptoms more than Depakote alone
        - Seroquel alone reduced depressive symptoms and suicidal ideation
    - Bipolar maintenance
        - Barzman, 2005 (funded by maker of Seroquel): Seroquel as effective as Depakote in adolescent bipolar disorder with disruptive behavior disorder.
        - Marchand et al, 2004: 200-600 mg/day, youth 7-15 yo, 0.1-12 months (average 6 months): 80% response
    - Aggression
        - Findling, 2006: study below extended 18 weeks more—safe and effective
        - Connor, 2006, treatment of adolescent conduct disorder, 7-week, RCT, placebo, pilot study, 19 youths, average dose 300 mg (range 150-450 mg): safe, effective and well-tolerated.
        - Findling, 2006: 8 week, open label, outpatient study in aggressive children with conduct disorder, 17 youth; aged 6-12 years of age; ~150 mg/day average—safe and effective
    - Schizoprenia
        - Several studies
        - Grecevich, 2001 and Shaw 2002: youths with psychotic disorders, 24 of 28 improved; reduced psychosis; ~300 mg/day; gained ~8 lb; slightly increased cholesterol
- Seroquel dosing
    - 25-100 mg improves sleep induction and continuity and increases total sleep time, sleep efficiency, % stage 2 sleep, and subjective sleep quality
    - 150-300 mg be effective for bipolar depression
    - 200-800 mg effective for mania; rapid dosing escalation (200 mg day 1, 400 mg day 2, 600 mg day 3) is generally well-tolerated and effective.
    - 400-800 mg effective for schizophrenia
- Overall summary of the side effects and risks include:
    - If for any reason you are dehydrated in the setting of taking Seroquel, let me know, as the combination of Seroquel and dehydration is more dangerous than dehydration alone
    - Sedation
        - 16-18% vs. 4% in placebo overall
        - 50% or more of patients when dose is more than 400 mg/day
        - 60% of youth patients. Provigil can help.
    - Dry mouth
        - 16% overall vs. 3% in placebo
        - 24% of youth patients
    - Muscle side effects; Nasrallah et al, 2006:
        - Acute: 13% Seroquel vs. 13% placebo
        - Chronic: 21% Seroquel vs. 19% placebo
        - Haldol: 60%
        - Lithium: 27%
    - Weight gain
        - 9% vs. 2% in placebo overall
        - 25% experience an increase in body weight of greater than 7% in 3-6 week trials
        - 8 pounds over 1 year
        - increased appetite in 8% of youth patients
    - dizziness
        - 7% vs. 3% in placebo overall
        - 36% of youth patients
    - headaches
    - agitation
    - stomach upset in 24% of youth patients
    - constipation
    - orthostatic hypotension (usually transient) in 7% of patients; 1% may faint with rapid escalation in dose.
    - transient and asymptomatic increases in liver enzymes.
    - slight increase in risk of seizures

- cataracts (in beagles; possible case reports in humans; not in monkeys; postmarketing surveillance has not revealed an increased rate in humans)
- a number of other side effects and risks in multiple organ systems
- does not appear to increase prolactin
- does not appear to cause problems with the heart or heart rhythm.
- 3 cases of thrombocytic thrombocytopenic purpura, 212 cases of leucopenia, neutropenia, thrombocytopenia, and anemia.
- Pregnancy
    - McKenna (2005) identified 36 prospective case studies without report of major malformations, and additional case reports support these findings (Grover et al, 2012)

- Pharmacodynamics, +
    - Mechanisms of action
        - Low affinity for D1, D2 receptors, both of which Seroquel blocks, and quick release from receptor
        - High affinity for D4 receptors, which they block; D4 receptors are more prevalent in the mesolimbic system which includes the mood circuitry, among other circuits).
        - Blocks 5HT 2a/6/7
        - Blocks histamine 1 and alpha 1 receptors
        - Increases indices of new neuronal growth in the anterior cingulated cortex, cerebellar vermis, and right ventral prefrontal cortex
    - Metabolized by 3A4; half life 7 hours; peak in 1-2 hours
    - Food--> increased peak and systemic exposure by 1.5-fold
    - Twenty metabolites; the 7-hydroxylated metabolite and the N-dealkylated metabolites are active; active metabolite may block norepinephrine reuptake
    - Comes in 25, 50, 100, 200 and 400 mg tabs; effective dose range 500-800 mg+/day. Half-life is 2-3 hours.
    - Also available as once-daily Seroquel XR