GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

### Week of October 31 - November 4, 2022

**SPOTLIGHT: Sertraline - How Effective is it for Depression Really?**

- Sober Up: Use of Gabapentin in Patients with Alcohol Use Disorder
- Shorter Labor: A Comparison of Pitocin Dosing Protocols
- Risk Factors for Suicide: Adopted vs Non-Adopted Individuals

# Sertraline: How Effective is it for Depression Really?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

**The Clinical Effectiveness of Sertraline in Primary Care and the Role of Depression Severity and Duration (PANDA): A Pragmatic, Double-Blind, Placebo-Controlled Randomized Trial**

Lewis G, Duffy L, Ades A, et al. The clinical effectiveness of sertraline in primary care and the role of depression severity and duration (PANDA): a pragmatic, double-blind, placebo-controlled randomized trial. *Lancet Psychiatry*. 2019;6(11):903-914. doi:10.1016/S2215-0366(19)30366-9



KEY TAKEAWAY: Although sertraline does not reduce depressive symptoms at six weeks, it significantly reduces depressive symptoms at 12 weeks.

STUDY DESIGN: Multicenter, double-blind, placebo-controlled randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Selective serotonin reuptake inhibitors (SSRIs) such as sertraline are widely prescribed in primary care as first-line treatment for depressive symptoms. These symptoms do not necessarily meet the diagnostic criteria for depression such as major depressive disorder. Previous research has been inconclusive regarding the overall effectiveness of SSRIs for the wide spectrum of severity and duration of depressive symptoms treated in primary care settings.

PATIENTS: Patients with depressive symptoms

INTERVENTION: Sertraline

CONTROL: Placebo

PRIMARY OUTCOME: Depressive symptoms

Secondary Outcomes: Anxiety, general mental health (e.g., psychological distress and well-being) and physical health

METHODS (BRIEF DESCRIPTION):

- Patients 18-74 years old with a mean age of 40 years old (59% female) were recruited by referral from 179 primary care practices in four cities in the United Kingdom.
- Their general practitioners identified patients with depressive symptoms of any severity or duration and acknowledged uncertainty about the benefit of antidepressant treatment.
- Patients were randomly assigned to the sertraline group or the placebo group.
- Patients received one capsule of either 50 mg sertraline or placebo daily orally for one week, followed by two capsules daily orally for up to 11 weeks. After six weeks they could increase to three capsules.
- At two weeks, six weeks, and 12 weeks, scores on the
  - Patient health questionnaire (PHQ-9)
  - Beck depression inventory (BDI-II)
  - Generalized anxiety disorder assessment (GAD-7)
  - Short form health survey of mental and physical health-related quality of life (SF-12).
  - Higher scores on the PHQ-9, BDI-II, and GAD-7 correspond to worsening symptom severity. Higher scores on the SF-12 signify better mental or physical functioning.

INTERVENTION (# IN THE GROUP): 266

COMPARISON (# IN THE GROUP): 284

FOLLOW UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- At six weeks, sertraline did not improve depressive symptoms compared to placebo (adjusted proportional difference [APD] 0.96; 95% CI, 0.86–1.1).
- At 12 weeks, sertraline significantly decreased depressive symptoms compared to placebo.
  - PHQ-9 depressive symptoms (APD 0.9; 95% CI, 0.8–0.97)
  - BDI-II depressive symptoms (APD 0.8; 95% CI, 0.7–0.95)

Secondary Outcomes –

- Sertraline significantly decreased anxiety compared to placebo as early as six weeks (APD 0.8; 95% CI, 0.7–0.9).
- Sertraline significantly improved the general mental health compared to placebo group over 12 weeks (APD 2.4; 95% CI ,1.1–3.7).
- The self-reported physical health between the sertraline and placebo groups was not statistically different.

LIMITATIONS:

- There was a possible halo effect (i.e., patients felt their anxiety symptoms improve, but reported it as depression symptoms improving).
- Medication adherence was self-reported, with no objective confirmation that the patients were taking the medications as recommended.

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# Sober Up: Use of Gabapentin in Patients with Alcohol Use Disorder

**Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients with Alcohol Withdrawal Symptoms: A Randomized Clinical Trial**

Anton RF, Latham P, Voronin K, et al. Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients With Alcohol Withdrawal Symptoms: A Randomized Clinical Trial. *JAMA Intern Med*. 2020;180(5):728-736. doi:10.1001/jamainternmed.2020.0249



**KEY TAKEAWAY:** Gabapentin compared with placebo significantly increases total abstinence and reduces drinking.

**STUDY DESIGN:** Double-blind, 16-week placebo-controlled randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to small patient size and high incompletion rates)

**BRIEF BACKGROUND INFORMATION:** Even though alcohol use disorder is widely recognized and about 30 million people meet the criteria for alcohol use disorder, only a small number receive appropriate pharmacotherapy. Patients are more likely to see their primary care physician for alcohol related problems such as cirrhosis, but not for their alcohol use disorder. Offering a personalized treatment plan may improve patient outcomes and efficacy of treatment

**PATIENTS:** Treatment-seeking individuals with alcohol use disorder

**INTERVENTION:** Gabapentin

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Heavy drinking days

Secondary Outcome: Total abstinence

**METHODS (BRIEF DESCRIPTION):**

- Male and female patients were included ranging from 18 to 70 years old and met DSM-5 criteria for alcohol use disorder.
- Included patients met the requirements of a minimum of five drinks for 90 days prior to randomization (determined by breath analyzer and urinary ethyl glucuronide testing).
- Exclusion criteria: use of psychotropic medication (except anti-depressants), active diagnosis of MDD, bipolar disorder, psychotic disorder, or eating disorder
- Patients with PTSD with stable symptoms were included given that alcohol use disorder is highly prevalent among those with PTSD.
- Participants had to be medically stable (liver enzymes less than 3 times upper normal limit).
- Women were excluded if pregnant or breast feeding.
- Woman were included if they were taking a reliable form of contraception or were post-menopausal.

**INTERVENTION (# IN THE GROUP):** 46

**COMPARISON (# IN THE GROUP):** 50

**FOLLOW UP PERIOD:** 16 weeks

**RESULTS:**

Primary Outcome –

- Gabapentin reduced the number of heavy drinking days compared to placebo as measured by %CDT (19% difference; 95% CI, 3.1–34; NNT=6).

Secondary Outcome –

- Gabapentin increased the number of no drinking days (total abstinence) compared to placebo as measured by %CDT (14% difference; 95% CI, 1.0–27; NNT=8).

**LIMITATIONS:**

- 30% of individuals on gabapentin and 39% on placebo did not complete the trial.
- Alcohol withdrawal symptoms were self-reported prior to the study.
- Participants with complex psychiatric and medical conditions, including history of alcohol withdrawal seizures, were excluded.

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# Shorter Labor: A Comparison of Pitocin Dosing Protocols

**High-Dose Compared with Standard-Dose Oxytocin Regimens to Augment Labor in Nulliparous Women**

Son M, Roy A, Stetson BT, et al. High-Dose Compared with Standard-Dose Oxytocin Regimens to Augment Labor in Nulliparous Women: A Randomized Controlled Trial. *Obstet Gynecol*. 2021;137(6):991-998. doi:10.1097/AOG.0000000000004399



KEY TAKEAWAY: Intrapartum high dose oxytocin significantly shortens labor time without increasing rate of delivery by cesarean in nulliparous White women ≥36 weeks gestational age.

STUDY DESIGN: Single site double blind randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: High dose intrapartum oxytocin has fallen out of favor as a method of labor augmentation, as there is conflicting evidence on the safety of high dose oxytocin regimens. However, there is insufficient evidence on whether it increases the risk of cesarean birth.

PATIENTS: Nulliparous women ≥36 weeks gestational age

INTERVENTION: High dose oxytocin augmentation

CONTROL: Standard dose oxytocin

PRIMARY OUTCOME: Cesarean delivery

Secondary Outcomes: Time to delivery, intrapartum chorioamnionitis, postpartum endometritis, postpartum hemorrhage

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria included nulliparous women ≥36 weeks gestation, singleton pregnancy, vertex position, in spontaneous labor, in need of oxytocin for labor augmentation, ≥18 years old, English speaking, no prior uterine surgeries, no cervical ripening methods used before oxytocin, and continuous fetal monitoring throughout treatment.
- Patients were randomized to high dose oxytocin (starting dose and intervals of six milliunits/min) or standard dose oxytocin (starting dose and intervals of six milliunits/min).
- Conducted at Northwestern Memorial Hospital which is a quaternary academic hospital in Chicago.
- Primary outcome measured was primary cesarean rates. Secondary outcomes measured were labor duration, chorioamnionitis, postpartum hemorrhage, endometritis, perinatal death, five-minute APGAR less than or equal to three, neonatal acidemia, NICU admission.

INTERVENTION (# IN THE GROUP): 502

COMPARISON (# IN THE GROUP): 501

FOLLOW UP PERIOD: Mothers were followed until hospital discharge; newborns were followed until hospital discharge or 28 days of life (whichever happened later)

RESULTS:

Primary Outcome –

- Cesarean delivery rate did not differ between high dose oxytocin vs standard dose oxytocin (15 vs 14; RR 1.0; 95% CI, 0.75–1.4).

Secondary Outcomes –

- High dose oxytocin decreased time to delivery by 1.4 hours (9.1 hrs vs 11 hrs; *P*<.001).
- High dose oxytocin decreased intrapartum chorioamnionitis (10 vs 16; RR 0.67; 95% CI, 0.48–0.92).
- No change in rate of postpartum endometritis (0.6 vs 1.0; RR 0.60; 95% CI, 0.14–2.5).
- No change in rate of postpartum hemorrhage (5.8 vs 4.6; RR 1.3; 95% CI, 0.74–2.1).

LIMITATIONS:

- Patients in the study were mostly White with commercial insurance at an academic center with low diversity, high level of available resources, and a high rate of operative deliveries.
- Secondary outcome assessment may be underpowered to detect the risk of complications.
- Possible Hawthorne effect.
- Overall, a lower incidence of cesarean delivery in this study than the national average; may not be applicable to other more diverse populations.
- Operative vaginal delivery outcomes not mentioned.

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# Risk Factors for Suicide: Adopted vs Non-Adopted Individuals

**Comparing Childhood Characteristics of Adopted and Non-adopted Individuals Deceased by Suicide**

Ligier F, Body Lawson F, Lamourette M, Giguère CE, Lesage A, Séguin M. Comparing Childhood Characteristics of Adopted and Non-adopted Individuals Deceased by Suicide. *Front Psychiatry*. 2022;13:756306. Published 2022 Jun 3. doi:10.3389/fpsyt.2022.756306



KEY TAKEAWAY: For individuals who were diagnosed with 12-month Axis I disorders well before suicide, adopted individuals deceased by suicide have a significantly higher incidence of Axis I and II disorders and significantly worse burden of adversity scores compared to non-adopted individuals deceased by suicide or living individuals.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: When compared to the general population, adoptees have a higher prevalence of mental disorders and a higher risk of suicide attempts. There are serious emotional, physical, and economic consequences with suicide and suicide attempts, with adoptees being more vulnerable to suicide. Therefore, it is important to assess the risk factors these individuals hold.

PATIENTS: Individuals deceased by suicide

INTERVENTION: Adopted individuals deceased by suicide

CONTROL: Non-adopted individuals deceased by suicide or living individuals

PRIMARY OUTCOME: Axis I and II disorders, childhood life events, and the burden of adversity scores

METHODS (BRIEF DESCRIPTION):

- 65 individuals were selected from a data bank of 700 suicide cases, consisting of 13 adopted individuals deceased by suicide, 26 non-adopted individuals deceased by suicide, and 26 non-adopted control living individuals.
- The selected individuals were between 14 and 84 years old, and 54% male. The mean age of suicide for adopted and non-adopted groups was 34 years old with a range of 13–83 years old.
- Suicide cases were identified from the coroner's office, and living controls were identified using a snowball sampling method.
- Adopted individuals deceased by suicide were matched (1:2) with non-adopted individuals deceased by suicide by province (Quebec, New Brunswick, and Ontario in Canada), age, gender, and time of death.
- For suicide cases, two structured interviews were conducted with the family of the bereaved 3–4 months after the suicide.
- Living control individuals were interviewed over the course of several months and an individual who knew the control individual was also interviewed.
- The interviews and medical files of the cases in each of the three groups were analyzed for the following risk factors:
  - 12-month DSM-IV Axis I disorders (just prior to suicide vs well before suicide): ADHD, mood disorder, anxiety disorder, substance abuse/dependence disorder, psychosis and schizophrenia, adjustment disorder, eating disorder, two or more disorders, and total with only one diagnosis (total number of individuals with only one recorded disorder).
  - DSM-IV Axis II disorders: Cluster A (paranoid, schizoid, schizotypal), B (antisocial, borderline, histrionic, narcissistic), and C (avoidant, dependent, and obsessive-compulsive personality disorders) personality disorders.
  - Early life events from 0–19 years old
  - The frequency severity, and duration of discipline/neglect/tensions in the parent-child relationship, sexual and physical abuse, academic difficulties, mental health problems, academic difficulties.
  - Burdens of adversity: scored by a panel of experts for each five-year period of an individual's life trajectory, ranging from severe (1–2), moderate (3–4), to low (5–6).

INTERVENTION (# IN THE GROUP): 13

COMPARISON (# IN THE GROUP): 52

FOLLOW UP PERIOD: 20 years

RESULTS:

- For individuals who were diagnosed with 12-month Axis I disorders well before suicide, adopted individuals deceased by suicide were significantly

more likely to have ADHD, two or more Axis I diagnoses, and Axis II Cluster C personality disorders than non-adopted individuals:
    - ADHD (adopted 3 vs non-adopted 0; *P*<.01)
    - Two or more Axis I diagnoses (7 adopted vs 3 non-adopted, *P*=.004)
    - Axis II Cluster C personality disorders (5 adopted vs 3 non-adopted, *P*=.*04*)
- For individuals who were diagnosed with 12-month Axis I disorders just prior to suicide, there were no significant differences in Axis I diagnoses between adopted and non-adopted individuals.
- Adopted individuals deceased by suicide had more severe burden of adversity than non-adopted individuals decreased by suicide in the following age groups:
    - Ages 0-4 (adopted 3.9 vs non-adopted 5.2, *P*=.01)
    - Ages 5-9 (adopted 3.4 vs non-adopted 4.5, *P*=.009)
    - Ages 10-14 (adopted 3.1 vs non-adopted 4.1, *P*=.02)
- Axis I mood disorders, substance use disorder, two or more Axis I diagnoses, and Axis II Cluster B and C personality disorders were reportedly more common in adopted individuals deceased by suicide than non-adopted living individuals. However, the significance of these differences was not reported.

LIMITATIONS:

- Recall bias can be unavoidable in retrospective cohort studies.
- The control non-adopted living individuals were not representative of the general population.
- No distinctions were made between domestic and international adoptees.

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